FDA Executive Summary DENXXXXX2

Prepared for the
March 21, 2024, Meeting of the
Ophthalmic Devices Panel

DENXXXXX2
FSYX™ Ocular Pressure Adjusting Pump (FSYX™ OPAP)
Balance Ophthalmics, Inc.

Introduction

This is the FDA Executive Summary for the FSYX™ Ocular Pressure Adjusting Pump (FSYX™ OPAP). The device is comprised of a set of goggles linked to a pump. When the goggles are worn, the pump creates negative pressure inside the space created by the goggles. The device is intended to serve as an adjunctive therapy for the reduction of intraocular pressure during nightly device use in adult patients with open-angle glaucoma and intraocular pressure (IOP) ≤ 21 mmHg.

On August 25, 2023, the sponsor submitted a De Novo classification requesting marketing authorization of the device under DENXXXXX2. This submission was reviewed by the Division of Ophthalmic Devices, Office of Health Technology 1, Office of Product Evaluation and Quality (OPEQ) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This document summarizes FDA's review of the De Novo request and highlights the areas for which we are seeking panel input.

Table of Contents

Tables

Figures

1. Proposed Indications for Use (IFU)

The sponsor has proposed the following Indications for Use (IFU) statement:

> *"The FSYX™ Ocular Pressure Adjusting Pump (FSYX OPAP) is indicated as adjunctive therapy for the reduction of intraocular pressure during nightly use in adult patients with open-angle glaucoma and intraocular pressure ≤ 21 mmHg."*

2. Device Description

The FSYX OPAP is comprised of two distinct elements, the programmable pump and the goggles with tubing, as shown in **Figure 1A and 1B**. The FSYX OPAP is designed to allow the application and monitoring of bilateral negative pressure (NP) in the microenvironment in front of a patient's eyes.

The FSYX OPAP goggles are designed to fit and seal around the eyes of patients, creating an air-tight chamber in which NP can be created and maintained. A headstrap is included with the goggles to facilitate reliable positioning on the patient's face during sleep. The goggles can be connected and disconnected from the FSYX OPAP pump to allow for daily cleaning. FSYX OPAP goggles should be replaced every 30 days.

The FSYX OPAP pump houses 2 miniature diaphragm pumps that produce programmable NP pressure levels independently for each eye. The pumps are connected to a manifold that pneumatically interfaces the connector integral to the tubing system of the goggles. The manifold also mechanically and pneumatically connects a plurality of pressure sensors and relief valves. To create NP for each goggle lens, a pump extracts air from the cavity created by the goggle and the patient's face. The pump is pneumatically connected to the goggle through a negative pressure line comprised of a tube, a portion of the connector, and a portion of the manifold. The air extracted from the goggle is evacuated from the FSYX OPAP pump through a pneumatic path integral to the manifold. For each individual goggle, there is a separate pump and NP line, which allows independent NP application treatments for each eye.

The NP inside each goggle is monitored by a pressure sensor that is pneumatically connected to the respective goggle through a sense line. The NP and sense lines for each goggle are pneumatically connected proximal to the goggle cavity; this ensures that creation and monitoring of the NP level in each goggle can occur independently. The signal from each sensor is used in a separate Proportional-Integral-Derivative (PID) control loop for each pump so that the applied NP matches the value entered by the treating physician. If leaks exist at the interface between the seal and the patient's skin, NP is reduced and the PID controller increases rotational speed of the pump to counterbalance the leak and reestablish the prescribed NP level.

An additional differential pressure sensor is connected to each of the two independent sense lines to ensure that the differential signal matches the arithmetic difference between the NP levels set

for the treatment of each eye and the actual NP levels sensed in each eye. An alarm is generated if the measured difference substantially departs from the arithmetic one.

For each independent NP line, a relief valve is also provided to mechanically limit the maximum allowable applied NP to a level < 40 mmHg.

The device is meant to be used at home, worn overnight while the patient sleeps. The “default” NP setting is -10 mm Hg for both eyes and the duration of NP is 8 hours. The allowable (i.e., programmable) range of duration is 1 to 12 hours and the allowable range of NP is -5 to -20 mm Hg.

2.1 FSYX OPAP Pump

The FSYX OPAP pump is comprised of the following sub-assemblies:

- Housing
- Touch screen
- Display board
- Main board
- RFID board
- 4G board
- Battery
- Manifold

The OPAP pump assembly includes the pump housing which includes a touchscreen/display for graphical user interface and interaction between user and device. Two mini diaphragm pumps are housed within the housing for creation of negative pressure levels independently for each eye. The manifold interfaces with goggle connector. The pump assembly includes the following circuitry boards: main, 4G and RFID. The RFID board will be de-activated for the proposed model.

The battery is located in the lower portion of the housing and is designed to supply at least 12 hours of uninterrupted therapy. The internal chambers and air paths of the connector are shown in **Figure 2**. The pneumatic diagram of the OPAP pump is shown in **Figure 3**. The manifold and goggle connector shows the internal chambers and air paths from pump to tube to sensors. The left negative pressure circuit is highlighted in red, the left sense line is highlighted in orange, the right negative pressure circuit is highlighted in blue, the right sense line is highlighted in purple, and the discharge path to atmosphere is highlighted in green.

2.2 FSYX OPAP Goggles

The goggles are available in 3 sizes (Small, Medium, Large) designed to create an air-tight seal around the eyes. The goggle assembly includes a headgear strap to facilitate wear during sleep. **Figure 4** provides an exploded view of all components of the goggle assembly.

Goggle lenses are cut from Uvex/Honeywell polycarbonate lens blanks and have an anti-fogging coating on the inside surface to prevent fogging during use.

Detailed images of the nose bridge, lens and lens pivot can be found in **Figures 5-7**. The nose bridge is deformable titanium sheet metal connected to the lenses by rivets with washers added for distribution of the load and grommets for an airtight seal. The cross-section image of the lens pivot shows with detail the connection of the outer tubing (sense line) and the inner tubing (vacuum line) to the eye cavity of the goggles. The pivot is designed to allow for rotation for comfort during wear.

The tubing system consists of external tubes with a smaller tube fitted inside the larger tubes. The cavity between the inner surface of the outer tube and the outer surface of the inner tube creates a pneumatic path referred to as the sense line. Each inner tube creates a pneumatic path referred to as the negative pressure line. The concentric tubing design prevents the sense line from collapsing before the negative pressure line when the tubing is kinked. If the sense line collapses before the negative pressure line, the pump would lose the negative pressure signal and could create excessive negative pressure in the goggles.

The goggle connector is designed with geometry for two main functions: (1) pneumatic connection of the sense lines and two negative pressure lines to the corresponding features of the manifold, and (2) mechanical connection of the connector to the OPAP pump device. The mechanical connection is designed to prevent connecting the goggles in the wrong orientation to the pump device.

The headgear consists of a stretchable strap with a longitudinal split, allowing it to be routed around the occipital and the parietal bones for a secure fit, and two buckles located temporally for the fitting and adjustment of the length of the strap.

2.3 Accessories and Related Devices

Other accessories used in conjunction with FSYX OPAP are:

- Wall charger
- USB cable
- Physician Application Software

The USB cable can be used to connect the FSYX OPAP pump to any compatible Windows computer for the purpose of programming NP therapy through the use of Physician Application Software (i.e., the Physician App).

The Physician App is Windows compatible software used by clinical staff to program the NP parameters (therapy duration and NP level for each eye) for the FSYX OPAP pump. In particular, the programmable values are the therapy duration, and the negative pressure level for each eye. The Physician App also downloads usage information from the connected pumps and saves it in a local database. The data are available to the physician for later review through the Physician App reporting functionality.

> ***FDA Commentary:*** *During review of the subject submission, FDA raised concerns regarding the cybersecurity controls related to the Physician Application. In response, the sponsor has elected to modify their device such that dedicated laptops will now be provided as part of their device. This dedicated laptop will include the Physician Application pre-installed with all internet, network and Bluetooth connections disabled. Please see* ***Section 5.3.1*** *below for additional details regarding cybersecurity testing.*

2.4 Excursion Goggles

To allow for the measurement of intraocular pressure (IOP) during the application of NP during the investigative clinical trials, the sponsor developed the Excursion Goggles (illustrated in **Figure 8**), which is a modification of their FSYX OPAP goggles. The Excursion goggles were utilized during in-office testing to facilitate IOP measurements with a Reichert Model 30 pneumatonometer during negative pressure application. All investigators and investigational site staff responsible for measuring IOP using the Excursion goggles and Reichert Model 30 pneumatonometer were trained by Equinox's clinical team.

The Excursion Goggles are designed with access ports on each lens, through which the excursion cartridge (silicone tube with latex Tono-Pen tip cover) is fitted. This set-up allows negative pressure (vacuum) to be maintained within the goggles during Model 30 pneumatonometry measurements.

Small, medium, and large sizes are provided to accommodate the variations in subject facial anatomy; dimensions are identical to the small, medium, and large FSYX OPAP goggles. **Figure 9** illustrates the Excursion Cartridge in yellow and the Tono-Pen cover in orange. **Figure 10** illustrates the use of the Excursion Goggles with Excursion Cartridge and Model 30 pneumatonometer. The latex Ocu-Film Tono-Pen tip cover was cleared in K070534 (blue colorant) and K882750 (no colorant). The Reichert Model 30 pneumatonometer is a cleared device (K002395).

2.5 Mechanism of Action

The sponsor hypothesized and stated the following in the submission regarding their proposed mechanism of action:

> *The FSYX OPAP's operation is based on Pascal's Law, which states that when there is a change in pressure at any point in a confined fluid, there is an equal change throughout the fluid. With the goggles properly situated over the eyes and NP applied via the programmable pump, there is a decrease in pressure applied locally to the eye, which results in a corresponding change to the pressure inside the eye.*

3. Target Condition and Available Treatment Options

Glaucoma is a group of diseases that damage the eye's optic nerve and can result in vision loss and blindness. Currently legally approved medical products in the US to lower intraocular pressure (IOP) include topical and oral medications, drug eluting implants, laser and surgical treatments, and permanent implants[1].

> ***FDA Commentary:*** *Legally currently marketed devices intended for the reduction of IOP are all either implants or surgical devices. All of these devices reduce IOP by either decreasing aqueous humor production or increasing aqueous humor outflow. The FSYX OPAP device is intended to reduce IOP during use by nightly application of negative pressure in front of the eye. This proposed mechanism of action for achieving reduction in IOP is different than that of any of the currently cleared/approved devices for patients with glaucoma.*

4. Regulatory History and Background Information

4.1 QXXXXX1 - Submitted September 8, 2017

The sponsor initially introduced their device as the Equinox Balance Goggles System (BGS) in a pre-submission submitted on September 8, 2017. The pre-submission was focused on their proposed non-clinical testing, clinical protocol, statistical analysis plan (SAP), and proposed future regulatory pathway. The sponsor also provided summaries of four prior clinical studies that were performed on earlier versions of the device (GEN0, GEN1) which were intended to serve as supplementary, not supportive, safety data. In FDA feedback, it was recommended that the De Novo process would likely be the most suitable regulatory pathway for the subject device. Additional recommendations/comments were sent to the sponsor regarding their clinical study related to the impact of eyelids on the measurement using the Excursion goggles, the primary effectiveness endpoint, patient reported outcomes, inclusion/exclusion criteria, the sample size, and the safety endpoints.

[1] https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/glaucoma#section-id-46

4.2 QXXXXX1/SXX1- Submitted April 3, 2018

On April 3, 2018, the sponsor submitted a follow-on submission to provide (1) a test plan with two bench studies to validate the IOP measurement method to be used in a future trial, (2) a revised clinical protocol based on the recommendations of the original pre-submission, and (3) to provide a revised human factors study plan. In QXXXXX1, FDA's feedback noted that the non-clinical testing proposed did not "demonstrate that the Model 30 pneumatonometer measurements through the Ocu-Film accurately measures the IOP of the eye with and without application of negative pressure". In response, the sponsor provided two bench study protocols ((1) Model 30 Measurements Without and With the Ocu-Film and (2) Model 30 Measurements with Varying Model Eye Pressures and BGS Negative Pressures.) Concerns were relayed to the sponsor regarding the bench studies, clinical protocol (i.e., enrollment of subjects on medication, appropriateness of endpoints), and human factors test plan (i.e., missing details from training plan, additional information needed for questionnaire).

4.3 DENXXXXX1- Submitted June 1, 2020

The sponsor officially submitted their initial De Novo for the subject device with the following Indications for Use (IFU) for their Mercury Multi-Pressure Dial (MPD) system:

> *"The Mercury Multi-Pressure Dial System is indicated for the reduction of intraocular pressure in adult patients with suspected glaucoma, ocular hypertension, or open angle glaucoma."*

In support of their application, the sponsor provided the results of their trial (Protocol CP-X10) titled "The Safety and Effectiveness of Negative Pressure Applied by the Equinox Mercury™ Multi-Pressure Dial to Lower Intraocular Pressure (IOP) in Adult Subjects (The Apollo Study)." This was a multicenter, prospective, randomized, controlled trial involving adults 22 or older with ocular hypertension (OHTN), diagnosis of glaucoma suspect (GS), or open-angle glaucoma (OAG) that was initiated on June 27, 2019, and completed on December 10, 2019. The planned duration of the trial was 90 days excluding the run-in phase, with study visits at Day 0, Day 30, Day 60, and Day 90. One eye per participant was randomized to be the study eye (i.e., receive negative pressure application with the MPD device) and the fellow eye was used as the control eye (i.e., without application of negative pressure). Participants were given MPD kits to take home and were trained by site staff on how to use the device. A two-week "run-in" phase was used to acclimate the participants to device wear. After the end of the run-in phase, adherence was assessed, and participants were randomized into the trial if the adherence criterion was met. Participants then were instructed to wear the MPD device overnight while sleeping at a negative pressure setting based on 60% of the pneumotonometry- based IOP. IOP was measured during in-office visits using Goldmann applanation tonometry (GAT) and pneumotonometry (using the Reichert Model 30 [M30] pneumatonometer) via the Excursion goggles. The results of this study were as follows:

- *Enrollment:* 91 participants were enrolled at six sites. Of these, 27 were screen failures. The two most common reasons for screen failure were 1) IOP was outside the required range of ≤ 32 and ≥13 mm Hg in both eyes and 2) unwillingness or inability to comply with study procedures, including in-home device use. Four (4) participants were discontinued after the run-in phase because they were unable to demonstrate an average of 3 hours of sleep wear per night across a minimum of 3 nights. 64 participants were randomized into the trial. Data from 58 participants were available for analysis at the Day 90 time point; 6 participants were discontinued due to withdrawal of consent due to difficulty with in-home device use, investigator decision, and reasons other than death.

- *Primary Effectiveness Endpoint:* The stated primary effectiveness endpoint was "The probability of eyes at the Day 90 visit with an IOP reduction (measured via pneumotonometry) ≥ 20% during the application of negative pressure (i.e., IOP reduction through the MPD ≥ 20% compared to IOP at the same visit without negative pressure)."

  Results: 52 of 64 (81.3%) study eyes (modified intent-to-treat population [mITT]) achieved at least 20% reduction in IOP, compared to two (2) of 64 control eyes (3.1%). The between-group percent difference was 78.1% (81.3% - 3.1% = 78.1%, 95% confidence interval [CI]: 58.5%, 93.0%) which was statistically significant (p <0.001). 18.8% of the study eyes (12/64) achieved <20% reduction. **Tables 1 and 2** illustrate that similar results were observed when the analysis was conducted on the Per-Protocol (PP) cohort. Statistical analysis demonstrates that there appears to be some variability to the response (degree of IOP lowering) in the study eyes. The response is more variable in the OAG sub-group compared to the ocular hypertensives and glaucoma suspects.

- *Safety Assessments:* The sponsor collected data on the following safety assessments:

  - Best-corrected distance visual acuity (BCDVA) loss (≥ 10 letters per ETDRS) (**Table 3 and 4**)
  - Biomicroscopic slit lamp and ophthalmoscopy findings (**Table 5 and 6**)
  - Visual Field mean deviation (MD) and pattern standard deviation (PSD) (**Table 7- 8**)
  - IOP measured by Goldmann Applanation Tonometry (**Table 9**)
  - Rate of ocular/periocular adverse events (% by adverse event) (**Table 10-14**)
  - Patient reported outcomes (SHPC-18 Instrument) (**Table 15**)

  - *Results:*

    - *Best-corrected distance visual acuity (BCDVA):* BCDVA worsening of ≥ 10 letters was reported in 3 study participants. Participant (b)(6) lost ≥ 15 letters of BCDVA in both eyes at Day 90 in association with ocular surface disease. With increased use of artificial tears, BCDVA returned to 20/20 within the following week. Two participants were reported with ≥

10-letter loss at Day 30. For Subject (b)(6), BCDVA worsening in the control eye was associated with worsening of cataract from Grade 1+ to Grade 2+. For Subject (b)(6), BCDVA loss was assessed using a Snellen (as opposed to EDTRS) chart; ETDRS assessment at the following visit indicated only a 2-letter difference from baseline.

- *Visual field (VF) testing:* This was performed at baseline, Day 30 and Day 90. Worsening ≥ 2.5 dB of the mean deviation (MD) parameter was reported cumulatively in 11 study and 11 control eyes. Pattern standard deviation (PSD) values remained fairly similar across timepoints.

- *Vertical cup-to-disc (C/D) ratio:* This was evaluated at baseline, Day 30, and Day 90. At Day 90, the proportion of eyes with an increase of ≤ 0.3 is 6.9% (4/58) in both groups. There were no reports of increase > 0.3.

- *IOP by Goldmann applanation tonometry (GAT):* IOP by GAT was measured prior to the use of the MPD/ negative pressure application and then measured again after the use of the MPD/ negative pressure. At Day 90, the mean difference in IOP by Goldmann applanation tonometry before and after negative pressure application was -1.09 mm Hg (-5.7% change) in study eyes and -0.94 mm Hg (-4.8% change) in control eyes (range, -5.00 mm Hg to +2.00 mm Hg [-26.3% to +14.3% change] in study eyes; -5.00 mm Hg to +3.50 mm Hg [-25.6% to +20.6% change] in control eyes).

- *Ocular and periorbital adverse events (AEs):* Ocular AEs were reported in 29.7% (29 AEs in 19/64) of study eyes and 17.2% (16 AEs in 11/64) of control eyes. None of these AEs were reported as severe. All of the lid edema, periorbital AEs, eye pain, and most of the change in dry eye signs/symptoms were attributed to the use of the device.

- *Symptoms and Health Problem Checklist (SHPC-18):* The SHPC-18 is a shortened version of the longer (43-item) questionnaire originally used in the Collaborative Initial Glaucoma Treatment Study (CIGTS). Items cover eye symptoms and visual function symptoms. The SHPC-18 was administered only at baseline and at Day 90. Equinox reports, “The largest increase in symptoms involved skin sensitivity around the eyes. The proportion of eyes with skin sensitivity around the eyes was 3.1% at baseline and 22.4% at Day 90 in study eyes. A similar increase was reported in the control group, i.e., 3.1% at baseline and 20.7% at Day 90. Also, the proportion of droopy eyelids increased from 9.4% at baseline to 19.0% at Day 90 in study eyes, compared to an increase from 9.4% at baseline to 12.1% at Day 90 in control eyes.” A few subjects reported “a little” or “somewhat” worsening of some visual function items, including blurry vision, difficulty with light transition.

There were a number of concerns regarding the preclinical and clinical testing that resulted in a request for additional information (**AINN deficiency letter** dated August 14, 2020) (see **Attachment 14**). The major concerns communicated in the **AINN letter** included the following:

- Request for validation of the IOP test measurement method used during the clinical study for evaluation of effectiveness.
- Insufficient clinical data to support the indication in the three clinical groups specified in the indications for use (IFU) - open-angle glaucoma (OAG), ocular hypertension (OHTN), glaucoma suspect (GS) - due to the following:
    - No sustained lowering of IOP has been demonstrated in the clinical trial over 90 days
    - For OHTN and GS, clinical study was under-powered
- Safety concerns
- Concerns regarding safe and effective programming of the device including unclear dose-response relationship
- Inadequate human factors testing to mitigate all risks to users
- Request for verification and validation of pump hardware
- Request for validation of goggle use-life
- Biocompatibility concerns
- Cybersecurity concerns

4.4 QXXXXX2- Submitted September 9, 2020

In response to the **AINN letter** sent on August 14, 2020, the sponsor submitted a Submission Issue Request (SIR) Q-submission to discuss the following deficiencies:

- Validation of IOP measurements from the Excursion Test Method (deficiency 1)
- Safety concerns for labeled use (deficiency 2)
- Device precision and IOP lowering effect (dose-relationship) (deficiency 3)
- Benefits to indicated population of lowering IOP temporarily each night (deficiency 4)
- Evidence to support GS and OHTN patients in IFU (deficiency 5)
- Mitigation of use-related risks from human factors validation (deficiency 7)

A meeting was held on September 30, 2020, to discuss these issues.

4.5 DENXXXXX1/SXX1- Submitted November 17, 2020

The sponsor submitted this supplement in response to the **AINN letter** sent on August 14, 2020. The sponsor provided non-clinical testing to address concerns regarding validation of the IOP test measurement method used during the clinical study, mitigation of risks in human factors testing, verification and validation of pump hardware, validation of goggle use-life and

cybersecurity concerns. As part of the evaluation of the sponsor's response to these deficiencies, the Agency remained concerned regarding the validity of the IOP measurements using the Excursion goggles and whether the reported data represented a true reduction of pressure inside of the eye.

In addition, the review team identified published articles regarding the subject device that were not known at the time of the review of the original De Novo submission. One study that was conducted evaluated IOP measurements using the "modified Excursion goggles" (*Ethier et al. Exp Eye Res. 2020 Feb:191:107928*). The other was an editorial opinion article written in response to the Ethier at al., 2020 study (*A. Sit, Editor's Selection, International Glaucoma Review, Issue 21-1*). In light of these new publications, the review team raised concerns regarding whether the data provided by the sponsor actually demonstrates an ***increase*** in IOP upon application of negative pressure. This concern that the goggle use results in an increase to IOP, rather than decreasing IOP to treat glaucoma patients, had potential impacts on the previously communicated concerns (deficiencies 2-5 from FDA **AINN letter** dated August 14, 2020) regarding the safety and effectiveness of the device. A **second AINN letter** was sent to the sponsor on January 6, 2021 (see **Attachment 16**).

FDA Commentary: *The Ethier et al. article (Ethier et al. Exp Eye Res. 2020 Feb:191:107928), evaluated a lumped-parameter mathematical model that was developed to explore the proposed mechanism of action of the FSYX OPAP device (referred to in the article by its previous name, MPD). The model predicted that NP application would cause a "relatively rapid increase in globe volume accompanied by increased blood volume in the eye" as well as a reduction of episcleral venous pressure "causing a slower adjustment of IOP due to altered aqueous humor dynamics." The authors also state:*

"The results of this study have valuable implications for understanding damage of retinal ganglion cell axons in glaucoma patients. If CSF pressure (CSFp) within the sub-arachnoidal space of the optic nerve and retrolaminar tissue pressure are unaffected by the periorbital negative pressure within the MPD goggles, then perforce the translaminar pressure difference must be reduced. Even if the MPD goggles expanded the optic nerve sheath and thus lowered the pressure of the retrolaminar CSF, the retrolaminar CSF is in communication with the relatively large volume of CSF not in the retrolaminar space (assuming the absence of a compartment syndrome).

FDA Commentary Cont'd:

As a proportion of the total CSF volume, putative expansion of the optic nerve sheath is a small volume, and thus such an expansion would not be expected lead to a large change in CSF pressure. The net effect should be beneficial, since a reduction in the translaminar pressure difference would reduce the biomechanical insult delivered to optic nerve head (ONH) tissues. However, it is also the case that increasing ocular (globe) volume will expand the scleral canal and transmit deformations to ONH tissues, albeit at lower pressures, which could increase the biomechanical insult that these tissues experience. It is known that these two effects differ in their relative importance from one person to another depending on scleral stiffness and optic cup shape, among other variables. For example, in some patients, the vitreoretinal interface moves anteriorly with an elevation in IOP, while in others it moves posteriorly. Ultimately, this model demonstrates a putative mechanism by which IOP can be reduced by lowering the periocular pressure, but the ultimate clinical benefit of the MPD for glaucoma patients must be determined by long-term clinical studies. The results presented in this report demonstrate a putative mechanism whereby application of negative pressure via a MPD can lower IOP, both when measured as a gauge pressure (pressure in the eye measured with reference to atmospheric pressure, i.e. absolute pressure – ambient pressure) and as an absolute pressure (pressure in the eye measured with reference to an absolute vacuum). We remark that IOP has historically been reported as a gauge pressure, whether determined by the most common, "gold standard" method of measurement, namely Goldmann applanation tonometry [GAT] (Kass, 1996), or other techniques such as manometry or wireless implanted IOP sensors. Such measurements could thus appropriately be referred to as the 'trans-corneal pressure difference.' Novel techniques, such as application of negative pressure by googles as reported here, will require careful nomenclature and interpretation of the meaning of IOP."

Traditionally, intraocular pressure (IOP) is assessed by the difference between the pressures inside and outside the eye. The eye is effectively a fluid-filled elastic bag where the pressure can be assumed to be the same throughout the intraocular space. However, the pressure outside the eye, differs based on the immediate environment. The cornea and surrounding sclera are normally exposed directly to the atmosphere, the back of the eye is surrounded by the tissues and fluids of the orbit, and the lamina cribrosa is exposed to optic nerve tissues and cerebrospinal fluid (CSF). The pressure exerted by these tissues and fluids usually approximates atmospheric pressure, but this balance can be upset by rapid changes in atmospheric pressure or by pathologic changes in CSF pressure.

Direct measurements of IOP are the most accurate but can only be made by direct contact between intraocular fluid and a pressure sensor, which requires invasive procedures to access the intraocular fluid. To avoid the risks involved in such invasive procedures, all routine clinical assessments of IOP are indirect surrogate measurements of resistance to deformation of the cornea. The most widely accepted is Goldmann Applanation Tonometry (GAT), which measures the static force required to press a circular piston against the cornea until a criterion area is flattened (see the upper right panel in the ***Figure 11****). Other common methods involve momentary deformation of the cornea by an air puff or the rebound behavior of a ballistic probe.*

FDA Commentary: *All of the above clinical measurement methods assume that the transcorneal pressure difference (TCPD) is equal to the IOP. Changes in IOP may be caused by changes to the amount of fluid in the eye and/or changes in the interocular volume. In almost all cases of IOP change, the exterior pressure on the eye is uniform and equal to atmospheric pressure (see the upper left panel in the* ***Figure 10****). Since intraocular fluid is incompressible, adding intraocular fluid increases both the IOP and intraocular volume. However, if the front of the eye is exposed to reduced (negative) pressure (see the lower left panel in* ***Figure 10****), the external pressure on the eye is no longer uniform because the pressure on the anterior segment is reduced (i.e., the TCPD is increased) while pressure on the posterior segment is still equal or nearly equal to atmospheric pressure. This unbalance can potentially pull the eye forward in the orbit and stretch the anterior segment resulting in the increase of the intraocular volume with no change in the amount of intraocular fluid, resulting in reduced IOP relative to atmospheric pressure. These potential secondary stresses on the anterior segment, retina, and optic nerve head are not associated with other existing methods for lowering IOP.*

In the case of the FSYX OPAP system, the environment immediately outside the eye is the applied NP, rather than atmospheric pressure. Therefore, in the sponsor's pivotal trial the conventional IOP is the TCPD relative to the within-goggle NP environment. The Panel will be asked to discuss the alternative measurement of IOP employed by the sponsor as it relates to the conventional IOP definition and whether the IFU adequately conveys the effectiveness of the device.

4.6 QXXXXX3 - Submitted February 19, 2021

The sponsor submitted a submission issue request (SIR) Q-submission following receipt of the January 6, 2021, **AINN letter**. The sponsor wished to discuss major deficiency 1 which identified several concerns about the safety of the device, specifically related to the concern that application of negative pressure (NP) may cause an increase in IOP. In addition to including a summary of the bench and clinical data provided previously in DENXXXXX1 and DENXXXXX1/SXX1, the sponsor provided preliminary data from the following new studies conducted with the device to demonstrate that the pressure inside the eye is decreasing during application of NP and to address FDA's safety concerns that an increase in transcorneal pressure difference (TCPD) may result in increased tension at the optic nerve that may result in worsening of glaucoma:

- Direct measurement of IOP: Living Eye Project
- Quantification of blood flow in retina, choroid and optic nerve by laser speckle flowgraphy (LSFG)
- CT scans of globe position
- Quantification of axial length and anterior chamber depth by Anterion OCT

- Spectralis OCT of optic nerve head (ONH)

In response to the information provided, FDA communicated (teleconference held on March 12, 2021) concerns that the data provided in these new studies did not adequately address the safety concerns previously conveyed (i.e., need for clinically significant biomarkers to assess for worsening glaucoma and ocular structure damage, evidence for use of surrogate evaluations). Comprehensive review of these new studies was performed inDENXXXXX1/SXX2 in which additional safety concerns were relayed to the sponsor as discussed in **Section 4.7** below (i.e., limited sample size, study design limitations).

4.7 DENXXXXX1/SXX2- Submitted August 17, 2021

In Supplement 2, the sponsor provided responses to the concerns communicated in the January 6, 2021, **AINN letter**. In response to the Agency's concern that the device might actually increase pressure during application of NP, the sponsor stated (p. 55) that "Equinox has always recognized that the TCPD with respect to the NP environment in the goggles increases in response to application of NP." The increase in TCPD with application of NP is stated to range from 21.7% to 26.9%. This observation was originally discussed by the sponsor in an article published in February 2020, prior to the June 2020 submission date of the original De Novo (Ethier, C. Ross ; Yoo, Paul ; Berdahl, John P, The effects of negative periocular pressure on intraocular pressure, Experimental eye research, 2020-02, Vol.191, p.107928-107928).

With regards to safety of the device, the sponsor provides a response to FDA's concern that 10.3% (n=4) of study eyes in the OAG group experienced worsening of visual fields with submission of the case narratives and visual field printouts for these 4 subjects. However, from FDA's perspective, the case narratives ruled out the possibility of glaucoma progression given that the visual field results show possible glaucomatous progression in the study eyes of at least three of the four participants, more so than in the control eye.

Additionally, in response to FDA's concern regarding the true physical effects of the negative pressure goggles on the effective IOP at the cornea and at the optic nerve head (i.e., increased tension at optic nerve and/or distension of the lamina cribrosa), the sponsor reports on an ongoing prospective, randomized study which captured OCT/OCTA imaging on glaucoma patients to evaluate the "true physical effects" of NP on various structural and vascular parameters of interest in adults (22 years or older) diagnosed with mild to moderate open angle glaucoma. The goggles were turned on and "ramped up" and "ramped down" at different NP levels (from 0 to 20 mmHg in 5 mmHg increments) lasting 2 minutes each across the entire range of available NPs. OCT imaging from 16 subjects was collected and OCT and OCTA images were collected on 12 subjects. Although the study reported no detectable lamina cribrosa movement (via a parameter called the "anterior lamina cribrosa depth" (ALCD)), FDA identified limitations of the design of this study, such as the duration of NP application did not mirror the expected clinical use, the small sample size, and the study did not functionally describe what is happening with the optic nerve during application of NP.

With regards to the device effectiveness, to demonstrate that the device does, decrease the pressure inside the eye during application of NP, the sponsor provides the following:

- Confirmation of the expected relationship between NP application and "absolute IOP" in a living donor model.
    - This study evaluated direct IOP measurements via a pressure transducer application of NP on a brain-dead organ donor. The eye of the one donor was cannulated and connected to a manometer setup. IOP was recorded in the following sequence:
        - for a period of 10 seconds before the MPD goggles pump was turned ON ("PRE")
        - for 120 seconds after the pump was turned ON ("PumpON")
        - for 120 seconds after the pump was turned OFF ("PumpOFF")
        - for 10 seconds after the BSS line was turned to the OPEN position ("POST")
- Investigation of the impact of external NP on the retrobulbar pressure in a full body cadaver model
    - The objective was to obtain direct measurements of pressures via manometry within the goggle space, inside the eye (IOP), and in the retrobulbar space behind the globe (RBP) prior to, during, and after NP application. IOP and RBP measurements were obtained from two eyes of two full body cadavers through a fluid catheter connected to a sensor. Both intra-ocular and retrobulbar pressures were measured directly through a fluid catheter. The IOP was measured by cannulating the posterior segment (i.e. vitreous chamber) of the subject with an 18Ga needle, and the RBP was measured by cannulating the retrobulbar space with a spinal tap needle (16Ga).
- Evaluation of intraocular blood flow prior to, during, and following NP application in normal and glaucoma subjects via laser speckle flowgraphy (LSFG).
    - The LSFG evaluation was obtained from an ongoing, prospective clinical study in 7 glaucoma eyes and 22 healthy eyes, which analyzed percent change in blood flow in the optic nerve head rim tissue, the retinal arterioles within the peripapillary zone, the area within the choroidal hypoperfusion zone, and the area outside the choroidal hypoperfusion zone is measured using LSFG before, during and after 5 minutes of negative pressure application (-15 mmHg).

From FDA's perspective, the long-term effects of extended repetitive periods of negative pressure application on the outflow mechanics of the trabecular meshwork and the autoregulation of IOP via the balancing of aqueous production and aqueous outflow rates have not been adequately investigated. Also, possible effects of long-term negative pressure application on anterior segment circulation (e.g., distension of conjunctival vessels and conjunctival hemorrhages have been observed) and corneal endothelial cell function (e.g., negative pressure could reduce the effectiveness of the endothelial cell pump that maintains a low stromal water concentration) have not been adequately studied. The probable benefits of a temporary ~5-10 mmHg IOP reduction at the back of the eye need to be balanced against the probable risks of

transcorneal pressure elevation of up to 15 mmHg in eyes whose mechanisms for autoregulation of IOP are typically already compromised.

In summary, the review team found that the non-clinical and clinical data provided failed to demonstrate a reasonable assurance of device safety and effectiveness for the proposed IFU to lower IOP in glaucoma patients, and the De Novo was declined (**DEND letter** dated September 10, 2021).

FDA Commentary: *FDA's perspective is that although the data from the living donor model and the full body cadaver model demonstrate that the application of NP results in a corresponding drop in measured internal pressure in the eye, these data are from limited samples (only 2 in each case) and do not represent the indicated device use (8 hours per night for several months).*

With regards to the LSFG, the blood flow measurements in the optic nerve head (ONH) are acceptable and demonstrate an increased blood flow during application of NP. However, the sponsor did not provide data to support LSFG-measured vascular resistance change as a biomarker for IOP change and the study fails to demonstrate whether ONH blood flow would remain increased during extended periods of applied NP (for example, autoregulation of ocular blood flow and the interactions between blood flow and IOP are continuous balancing acts that may vary in significant ways over the long term that cannot be detected by acute measurements).

In the sponsor's current De Novo (DENXXXXX2) the sponsor clarified that the LSFG study was not intended to demonstrate that improved blood flow prevents progression, rather it was to "demonstrate that observed changes in blood flow are incompatible with the concern that NP applied to the front of the eye increases IOP".

4.8 QXXXXX4- Submitted January 4, 2022

Following the **decline letter**, the sponsor submitted a Q-Submission (QXXXXX4) to obtain more information related to their proposed testing and Indications for Use for a future De Novo. In the cover letter for this pre-submission (dated January 3, 2022), the sponsor stated that the purpose of the submission was "to obtain input from the Agency, and its Network of Experts (NoE), to align on evidence (i.e., empirical data and test methods for data collection) needed to address the questions in the **decline letter** and further demonstrate that the benefits of the MPD outweigh the risks for the proposed indication for use (IFU)." To satisfy the sponsor's request to have a "NoE" provide comments, the FDA sought input from four Special Government Employees (SGEs) with expertise in glaucoma. The Agency requested input from the SGEs on questions related to topics relevant to address the specific questions posed by the sponsor (e.g., the wording of the IFU, safety and effectiveness concerns (i.e., potential for worsening of glaucoma), and the OCT/OCTA study).

In this pre-submission, the sponsor provided a protocol synopsis for CP-X19 (a clinical study ongoing at the time of the submission of QXXXXX4), along with other supplemental studies (i.e., OCT/OCTA supplemented by a finite element model quantifying stress/strain). Additionally, the sponsor proposed the following modified IFU to address deficiencies from the DENXXXXX1/SXX2 **decline letter**:

> *"The Mercury Multi-Pressure Dial System is indicated for the reduction of intraocular pressure in adult patients with suspected glaucoma, ocular hypertension, or open angle glaucoma."*

FDA sent feedback to the sponsor (**letter** dated April 29, 2022, **Attachment 22**), which took into consideration the feedback from the SGEs. From FDA's perspective, the supplemental study testing & protocol synopsis for CP-X19 did not appear sufficient to address the concerns previously communicated in the DENXXXXX1/SXX2 **decline letter** and therefore FDA recommended that the sponsor conduct a new clinical study. Furthermore, the sponsor was notified that the IFU would need to be supported by the outcomes of their clinical study. The issues highlighted in CP-X19 include the use of post-hoc analysis to assess for glaucoma progression, lack of clarity on how NP settings were programmed particularly with regard to sleep-lab IOP assessments, missing details on adverse events and corresponding NP settings, and outstanding questions on the device benefit. In addition to the response to the sponsor's specific questions in our April 29, 2022, feedback, the sponsor was also sent the complete responses from the SGEs at the sponsor' request.

A meeting was held on May 5, 2022, during which the sponsor sought FDA agreement on the appropriate safety and effectiveness parameters for the new clinical study that FDA is recommending. In this meeting, the FDA encouraged the sponsor to submit a clinical study protocol for review in a supplement.

4.9 QXXXXX4/SXX1- Submitted June 16, 2022

The sponsor submitted this supplement (QXXXXX4/SXX1) to request feedback related to a new proposed clinical trial (CP-X24) protocol. Additionally, to address the FDA and SGE feedback provided in QXXXXX4, the sponsor proposed the following revised IFU:

> *"The Mercury™ Multi-Pressure Dial System is indicated as adjunctive therapy for the reduction of intraocular pressure, relative to atmospheric pressure, during use in adult patients with open-angle glaucoma."*

FDA sought feedback from 3 of the 4 same SGEs as QXXXXX4 to provide recommendations to the specific questions from the sponsor. Based on the team's review of the file, with consideration of the feedback from the SGEs, FDA provided comments to the sponsor on August 26, 2022, with recommendations regarding the proposed clinical protocol and the proposed approach of supplementing these data with data from a study of the device in normal tension

glaucoma (NTG) patients (CP-X19, the clinical study provided in the subject submission). The feedback noted that:

- The proposed study (CP-X24) was not powered (i.e., inadequate sample size) to detect changes to clinically relevant safety outcomes
- The enrollment criteria did not adequately define the population in which the device should be used
- The different sub-populations (sub-types of OAG, different baseline IOPs, etc.) were not adequately represented in the proposed study
- The methods for collecting and evaluating the clinical assessments (for both safety and effectiveness) were not sufficiently described/robust
- The impact on the eye from use of the device per the labeling (8 hours per night for long-term use) was still not adequately addressed by the proposed study and the NTG study
- The dose response remained unclear
- The protocol did not analyze changes to the TCPD
- The Patient Reported Outcomes (PROs) were omitted from the proposed study

The sponsor sent an email on August 30, 2022, requesting cancellation of the scheduled meeting to discuss the Agency's feedback.

FDA Commentary: *While the sponsor received FDA feedback for CP-X24 in QXXXXX4/S001, the results provided in support of the subject De Novo (DENXXXXX2) were from their CP-X19 trial, which had been ongoing during the review of QXXXXX4. CP-X19 was initiated in 2020 (first participant screened in January of 2020).*

It should be noted that, as described in ***Section 8*** *below, the sponsor did provide results from a study with the protocol number "CP-X24" as part of their response to Deficiency 4.a.i of the* ***AINN letter*** *dated November 8, 2023 (for the subject De Novo). However, "CP-X24" study is a study measuring IOP with manometry in 17 cataract surgery patients who used the device shortly before cataract surgery and is not the same study as reviewed by the Agency in QXXXXX4/SXX1. Please note that FDA did not provide any pre-submission feedback on "CP-X24."*

4.10 DENXXXXX2- Submitted August 25, 2023

After obtaining FDA feedback through the sponsor's previous De Novo (DENXXXXX1) and subsequent pre-submissions, the sponsor provided the non-clinical testing submitted in DENXXXXX1 and the results of a clinical study (CP-X19). The sponsor stated that "*The FSYX Ocular Pressure Adjusting Pump (FSYX OPAP) is identical to the Mercury™ Multi-Pressure Dial (MPD) System described in DEN XXXXX1 and all bench, non-clinical and clinical data in*

DENXXXXX1 previously reviewed and determined to be acceptable by Agency personnel applies to the FSYX OPAP." In their submission, the sponsor requested the device be brought before the Ophthalmic Devices Panel of the Medical Devices Advisory Committee to solicit recommendations on the safety and effectiveness of their device from external experts. The sponsor proposed the following IFU:

> *"The FSYX™ Ocular Pressure Adjusting Pump (FSYX OPAP) is indicated as adjunctive therapy for the reduction of intraocular pressure during use in adult patients with open-angle glaucoma and IOP ≤ 21 mmHg."*

FDA Commentary: *The IFU differs from Equinox Ophthalmics prior De Novo (DENXXXXX1) in that it is now indicated as "adjunctive therapy" and in OAG glaucoma patients with IOP ≤ 21 mmHg.*

The clinical trial (CP-X19) provided in support of this submission was intended to demonstrate the safety and effectiveness of the FYSX OPAP as an **adjunct treatment for lowering IOP, during use, in patients with normal tension glaucoma (NTG)** over the course of **52 weeks**. In CP-X19, a total of ninety-four (94) participants met eligibility criteria and were randomized and **sixty-two (62) randomized participants** completed the study. The following notable clinical issues were identified in CP-X19 and were communicated to the sponsor in an **AINN letter** sent on November 8, 2023:

- Uncertainty over whether the use of the device may worsen glaucoma
- Use of a Reading Center (RC) post-hoc to analyze glaucoma progression using VF and OCT data
- Worsening of glaucoma was not pre-specified as an anticipated adverse event (AE)
- Definitions of what constitutes worsening of glaucoma were not pre-specified
- Safety population arbitrarily defined at the time of randomization
- Higher rate of AE occurrences appear to be associated with increase of NP setting
- Participants unable to tolerate daily (or nightly) wear of more than 5 or 6 hours at all time points
- Investigator's programming of NP settings is unstandardized for most of the trial
- Transcorneal pressure difference [TCPD] values & calculations not provided

The **deficiency letter** also identified concerns related to several non-clinical test reports.

4.11 DENXXXXX2/SXX1- Submitted January 3, 2024

The sponsor provided their response to the FDA **AINN letter** dated November 8, 2023.

The sponsor has revised their IFU to specify the device is intended for "nightly use". The currently proposed IFU statement is as follows:

*"The FSYX™ Ocular Pressure Adjusting Pump (FSYX OPAP) is indicated as adjunctive therapy for the reduction of intraocular pressure during **nightly use** in adult patients with open-angle glaucoma and intraocular pressure ≤ 21 mmHg."*

FDA Commentary: *The sponsor modified the IFU in response to deficiency 4.a.ii of the **AINN letter** dated November 8, 2023.*

The Panel will be asked to discuss whether the language "reduction of IOP" in the IFU accurately describes the function of the device.

5. Non-Clinical Studies

5.1 Biocompatibility

Biocompatibility testing was performed on the OPAP by separating the components into three test groups: polymeric components, elastomeric components, and all components. The sample sets are as follows:

- Sample Set A consisted of the right seal (large), left seal (large), headstrap buckle, and para-tube tubing (polymeric components).
- Sample Set B consisted of the headstrap (elastomeric component).
- Sample Set C consisted of right seal (large), left seal (large), headstrap buckle, para-tube tubing, and headstrap (all components).

The biocompatibility assessment was performed in accordance with International Standard Organization (ISO) 10993-1: Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process, Part 5: Tests for in vitro cytotoxicity, - Part 10: Tests for skin sensitization. All tests were performed in accordance with Good Laboratory Practices (GLP).

FDA Commentary: *The FDA found the biocompatibility information to be adequate.*

5.2 Sterilization, Packaging, and Shelf-Life

The device is provided as single-patient, multi-use and non-sterile; therefore, there is no sterility/shelf-life associated with the device. The use-life of the components are defined as follows:

- Pump – 5 years
- Battery – 500 cycles

- Goggles – 1 month

The labeling provides recommended instructions for cleaning of the goggles and OPAP pump unit. The sponsor provided testing to support the transport stability, the labeled shelf-life, and labeled cleaning instructions. The packaging requirements are compliant with standards ASTM D4169 and ISTA 2A.

FDA Commentary: *FDA originally reviewed the test reports for the sterilization, packaging and shelf-life in DENXXXXX1 and found the results acceptable. No changes made to the device in the current De Novo impacted the prior assessments, and they remain acceptable.*

5.3 Software/Firmware & Cybersecurity/Interoperability

5.3.1 Cybersecurity

The OPAP Physician's Application is a PC-based application used by a physician to program a pump's treatment settings via a USB-C connection. The procedure for a physician to program the pump include the verification of settings by confirmation on the device itself. The software resides on a platform that allows for external connections: Wi-Fi (WLAN), Bluetooth and wired connections: Ethernet (LAN), USB. The purpose of these communications is to control the device (including device treatment settings). Use of Public Networks is possible. No user accounts are on the application; user account and privileges are to be handled by the physician office's IT processes.

FDA Commentary*: The sponsor provided cybersecurity risk assessments that almost solely relied on physical access to the device and software as a form of risk mitigation to ensure cybersecurity. No controls were implemented for a minimum system requirement or security requirements and all installation and systems security were left to the physician office's IT. These factors leave both the OPAP Pump and Physician Application vulnerable to cybersecurity attacks due to potentially unsupported operating systems, lack of proper malware protection, inadequate systems support, and possible physical tempering with lack of any real hardening practices. It should be noted that new cybersecurity laws (the Consolidated Appropriations Act, 2023 "Omnibus") were passed on December 29, 2022 subsequent to FDAs review of the sponsors first De Novo submission (DENXXXXX1). The new law includes requirements for new rigorous cybersecurity controls and vulnerability and penetration testing as part of proper cybersecurity measures for medical devices. Therefore, the sponsor's current measures and documentation for cybersecurity is* ***inadequate*** *and does not support proper cybersecurity requirements. FDA requested the sponsor to address these concerns as part of our* ***AINN deficiency letter*** *dated November 8, 2023.*

The Panel will not be asked questions regarding cybersecurity*.*

5.3.2. Software

- Software/Firmware Version:
    - FSYX™ OPAP Pump: v0.03:846
    - FSYX™ OPAP Physician App: v0.03:901

The sponsor has classified their documentation level as "Enhanced Documentation" for both the FSYX OPAP Pump and the FSYX OPAP Physician App. The sponsor provided OPAP Pump firmware and Physician App software documentation, outlining the software description, architecture, design specifications, risk assessments, and verification and validation testing to ensure proper system functions and essential performance are met.

5.4 EMC, Wireless, Electrical, Mechanical, and Thermal Safety & Risk Analysis

FDA Commentary: *Proper OPAP Pump firmware and Physician App software documentation was provided, outlining the software description, architecture, design specifications, risk assessments, and verification and validation testing to ensure proper system functions and essential performance are met. However, no software maintenance practices plan documentations or proper declaration of conformity (DoC) to either "ANSI AAMI IEC 62304:2006/A1:2016" or "IEC 62304 Edition 1.1 2015-06 Consolidated Version" was provided in DENXXXXX2. This issue was communicated to the sponsor in an* ***AINN deficiency letter*** *on November 8, 2023.*

The Panel will not be asked questions regarding software.

Testing was provided to address the electrical safety, pump life, electromagnetic compatibility, battery capacity/transport/safety, and Radio Frequency Identification (RFID) immunity, in support of the OPAP.

FDA Commentary*: During review of the EMC and ES test reports, safety concerns were noted regarding the following claim related the subject device: "The Gen2 BGS shall not generate pressure below -40 mmHg for longer than 10 seconds". The sponsor did not provide any test results or justifications within the submission that demonstrates that this maximum allowable NP is safe for any period of time (i.e., 10 seconds). Given that the maximum NP was not adequately validated, and the device operational pressure range is -5 mmHg to -20 mmHg, this concern was communicated as deficiency 10 in the* ***AINN deficiency letter*** *dated November 8, 2023.*

FDA Commentary Cont'd: *In DENXXXXX2/SXX1, the Sponsor provided a risk management DOC that clarified that "the relief valve sits in the pneumatic path and is intended to relieve pressure at 30mmHg, well below the 40mmHg indicated in the potential hazard; thus, should the system achieve 30mmHg, the valve unseats, allowing ambient air to fill the pneumatic path and restore pressure."*

Additionally, the Sponsor also explained that based on design of the device system that includes safeguards to regulate the pressure, they estimated a low likelihood (probability of 4 in 1e9) of the device reaching -40 mmHg. Also, from the software perspective, the software has limits in place so that the physician cannot program the treatment for anything outside -5 mmHg to -20 mmHg.

The sponsor did not provide testing to address EMC disturbances from potential common RF emitters. Lastly, concerns were raised regarding the conflicting software versions found throughout the documentation. It is unclear from this discrepancy if the device the testing is performed on differs from the device that is intended to be marketed. These concerns were relayed to the sponsor in an ***AINN deficiency letter*** *on November 8, 2023.*

The Panel will not be asked questions regarding EMC, Wireless, Electrical, Mechanical, and Thermal Safety & Risk Analysis.

5.5 Human Factors

A formative usability study followed by a summative label comprehension and usability study was conducted to assess human factors for the subject device.

FDA Commentary: *The FDA reviewers found the human factors information to be* ***adequate.***

5.6 Bench Testing

5.6.1 Testing on OPAP Pump

The following tests were provided in support of the performance of the OPAP Pump:

- Verification and Validation testing verified that the OPAP Pump met the performance criteria defined in the Product Requirements Specification document.
- Pressure Release Valve Cycle Test testing was performed on 3 pressure release valves to verify the regulated release pressure of the valve and demonstrate over 100,000 pressure release cycles (per IEC 60601 section 9.7.7(h)).
- Over Pressure Valve Flow Test was conducted to verify that the design of the relief valve and the manifold it mounts into is such that, when the valve is activated, the system will provide the flow capacity to keep the system at or above -40mmHg.

***FDA Commentary**: The testing on the OPAP Pump was considered acceptable.*

5.6.2 Testing on OPAP Goggles

The following tests were provided in support the performance of the OPAP Goggles:

- Goggle Verification-Mechanical Integrity Testing was performed to document that the design of the goggles meet all requirements documented in the MPD Goggles Specifications in PS-012, including:

    - Formation of a hermetic seal to the respective left and right lenses.
    - The strength of the vacuum and sensor tube joint at the connection to the lens and at the connection to the connector to withstand 6 lbs, the force exerted on the tube assembly by the pump from a 3.5 ft free fall.
    - Maintenance of vacuum from -5 mmHg to -30 mmHg with a leak rate no greater than 0.5 mmHg per second during application of 6 lbs on all joints.
    - Maintenance of Goggle seal for treatment range of -5 mmHg to -30 mmHg.

    Goggle Kink Resistance testing was conducted to evaluate the kink resistance of the goggle tubing to verify the safety of the design of the co-axial tubing while there is a kink in the tubing. Additionally, testing demonstrates that the inner vacuum line, by design, becomes occluded before the sensor line in a kink scenario. This would prevent the vacuum pump from running beyond the target set-point, since the pump assembly senses the pressure in the goggles and therefore has the ability to regulate the pressure as intended. The angle under which a kink will be formed in both the sensor line and the vacuum line were tested to observe when each line becomes restricted when kinked.

***FDA Commentary:** The FDA review team found that the testing provided to validate the OPAP Goggles was adequate.*

5.6.3 Testing on OPAP System

Design Verification testing was performed to document the verification and validation assessment for the Equinox Multi Pressure Dial (MPD Gen 2) system against the specifications outlined in PS-008 Equinox MPD Product Requirements including:

- Independent control of pressure for each goggle within ±1 mmHg.
- Exposure to pressure of -40 mmHg shall not exceed 10 seconds.
- Logging patient usage and compliance data gathered over a period of six months of daily 8-hour usage.

- Noise level of ≤40 Db at 1 meter distance during treatment with no leakage through the goggles seals.

FDA Commentary: *The FDA review team found that the testing provided to validate the OPAP System was adequate.*

5.6.4 Testing on Excursion Goggles

Validation testing was conducted to verify the accuracy of the Excursion Goggles for measuring the pressure in the eye during NP application. Testing demonstrated that, over a range of pre-set IOPs in an eye model (5 to 30 mmHg) and application of a range of NPs (-5 to -20 mmHg), the measurement of IOP with the Excursion Goggles (through the ocu-film and closed eyelid) was comparable to the IOP measured in the test eye on a transducer. The mean difference between the Excursion Test Method and the transducer IOP measurements when considering all 520 paired measurements from all the test configurations was 0.72 mmHg, with 89% of paired measurements within 2.5 mmHg and 100% within 4.0 mmHg.

FDA Commentary: *The FDA review team found that the testing provided to validate the Excursion Goggles was adequate.*

6. Clinical Trial Design

Protocol CP-X19 (called the "Artemis Study") was a prospective, multicenter, randomized clinical trial that began on January 21, 2020 (under protocol revision 3) and ended on October 20, 2022. The overall design is similar to that of the CP-X10 pivotal trial reviewed under DENXXXXX1. Adults age 40 or older with a diagnosis of normal-tension glaucoma (NTG) were enrolled. Evaluation of eligibility was conducted on what was designated as Day -14 of the trial. Eligible participants who were on IOP-lowering medications and who did not have documentation of unmedicated IOP ≤ 21 mm Hg at the time of screening were instructed to undergo a 30-day washout of those medications (note that once washout is completed and a unmedicated baseline IOP was determined, the participant could resume IOP-lowering medications). Those who had unmedicated IOP ≤ 21 mm Hg after washout were allowed to continue in the trial. After completion of washout, participants were then instructed to begin at-home use of the FYSX device for a "run-in" phase (Day -14 to Day 0). Training on the home use of FYSX was provided on Day -14. One week into initiation of device use, participants were requested to follow up for Visit 2 (Day -7) to address any home-use issues and to allow for assessment of wear time (using data downloaded from pump) following the first week of device use. On Day 0 (Visit 3), one eye of each eligible participant was randomized to receive negative pressure application with the FYSX device. The fellow eye was used as a control eye. A wear schedule of approximately 6 hours per night, 5 nights per week was recommended to

participants. Some scheduled IOP assessments were planned for measurement in a sleep lab. Various scheduled IOP assessments for key effectiveness endpoints were planned to be performed with Goldmann applanation tonometry at the slit-lamp biomicroscope and with pneumotonometry through the "excursion goggles." The planned duration of the trial was 1 year (52 weeks). 165 participants were enrolled across 11 sites in the United States. 55 of 165 (33.3%) failed screening and 110 participants participated in a "run-in" phase prior to randomization. 4 of the 110 (3.6%) participants who participated in the "run-in" phase were exited because they were unable to achieve the minimum sleep-wear requirement of an average of ≥3 hours across at least 3 nights of a consecutive 7-day run-in period between Visits 2 and 3. Another 4 of 110 (3.6%) exited due to concerns about sleep lab availability during the COVID-19 pandemic. 106 participants returned for Visit 3 (Day 0) and 8 of 106 (7.5%) were either found ineligible or withdrew consent. This resulted in 94 participants randomized. One participant was found ineligible after randomization and exited. Of these remaining 93, 60 (64.5%) completed the Week 52 visits with no major protocol deviations; 31 exited prior to Week 52 and 2 were reported with major protocol deviations.

FDA Commentary: *Please note that the protocol underwent several revisions after the trial was initiated on January 21, 2020.*

Significant changes to the protocol made in Revisions 5 and 6 (the latter is the final version of the protocol) are summarized below:

- *Adjusted post-randomization NP programming from a prescribed method to be at the investigator's discretion (Revision 5 [May 17, 2020])*
- *Removed requirement for a sleep lab visit in conjunction with the Week 26 Visit (Revision 6 [November 10, 2021])*
- *Added requirement for report visual field testing if MD worsening was noted to be ≥ 2.5 dB in comparison with Baseline (Day -14) (Revision 6)*
- *Removed plan for an interim statistical analysis based on Week 26 data (Revision 6)*

In Deficiency 1.c of the FDA ***AINN deficiency letter*** *dated November 8, 2023, raised the concern that the requirement to report mean deviation (MD) worsening ≥ 2.5 dB was added almost 23 months after the initiation of the trial. The introduction of this revision after a significant portion of the trial had already been ongoing raises concern that VFs may not have been analyzed by investigators with adequate robustness. This late modification to the protocol may introduce uncertainty as to how glaucoma worsening was assessed during the trial.*

FDA Commentary Cont'd: *In response to Deficiency 1.c, the sponsor acknowledged that the trial was not designed to assess glaucomatous progression. To minimize the potential bias from the post-hoc nature of the VF/OCT analysis, the sponsor requested that an independent third party, the University of Iowa Visual Field Reading Center (VFRC), perform a masked assessment of VFs for CP-X10 and CP-X19 participants. The sponsor stated, "While the analysis performed by the VFRC was post-hoc, the VFRC used best practices for review and analysis of all VF and OCT data obtained in CP-X10 and CP-X19. Three senior visual field readers masked to treatment assignment participated in the analysis of data provided. Each participant's visual field and OCT examinations were refined by evaluating for reliability, abnormal performance measures, and presence of characteristic perimetric and/or OCT artifacts."*

The sponsor also stated that Revision 2 of the CP-X19 protocol (dated December 3, 2019); implemented prior to participant enrollment) required VF testing and OCT imaging of the optic nerve head and retinal nerve fiber layer (RNFL) measurement at the baseline, Week 26, and Week 52 time points. In Revision 6 of the protocol (November 10, 2021), additional specifications were added to "maximize visual field reliability." Please refer to ***Section 7.5.4*** *for further details.*

6.1 Enrollment Criteria

The study cohort consisted of participants who met the following eligibility criteria.

6.1.1 Inclusion Criteria

Patients who met the following criteria were considered for inclusion in this trial:

1. Male or female ≥ 40 years of age at the time of signing the informed consent
2. Willing to sign the informed consent and capable of committing to the duration of the study
3. Orbital anatomy permitting a proper seal in both eyes when goggles are placed over eyes such that IOP measurements can be measured with Excursion Goggles in place
4. Diagnosis of NTG confirmed by glaucomatous optic nerve head or retinal nerve fiber layer structural abnormalities and/or VF abnormalities (from threshold VFs performed within 60 days prior to Visit 1) and:
    a. no documented unmedicated IOP > 21 mmHg in either eye, or
    b. in the absence of documented unmedicated IOPs, with unmedicated IOP ≤ 21 mmHg in both eyes following ocular hypotensive medication washout
5. Baseline IOP ≥ 12 mmHg and ≤ 21 mmHg (measured using GAT) in both eyes at Visit 1 (or Visit 1a, if applicable)
6. Literate, able to speak English, Spanish, or Japanese, and able to understand and follow study instructions

7. Demonstrate the ability to successfully average ≥ 3 hours of sleep wear of OPAP goggles during at least 3 nights of a consecutive 7-day run-in period (between Visit 2 and Visit 3)

6.1.2 Exclusion Criteria

Patients who met any one of the following criteria were excluded from this trial:

1. History of allergy to primary study device material (i.e., silicone and latex)
2. History of any ocular disorder or condition (e.g., corneal transplant) in either eye that would likely interfere with the interpretation of the study results or compromise subject safety
3. Prior or active retinal tear/detachment, unresolved cystoid macular edema, wet macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, or any other fundus findings that may prevent visualization of the retina in either eye
4. History of prior penetrating filtering (i.e., trabeculectomy) or tube/shunt glaucoma surgery in either eye (this does not include subjects with minimally invasive glaucoma surgery (MIGS) procedures or implants)
5. Narrow anterior chamber angle anatomy in either eye as visualized by gonioscopy with a Shaffer angle grade of ≤ 2 in any of the four quadrants
6. Eyelid edema, festoons, or excessive skin laxity in either eye
7. Uveitis or conjunctival chemosis in either eye
8. Best corrected distance visual acuity of 20/200 or worse in either eye
9. In the opinion of the investigator, may require any ocular surgery (e.g., cataract extraction or glaucoma procedure, including SLT) in either eye during the course of the study
10. Do not wish to or cannot comply with study procedures, including home use of the study device

6.2 Visit Schedule/Clinical Assessments

Figure 12 depicts the Study Visit Flowchart.

Participants who provided informed consent were preliminarily evaluated for eligibility during a Baseline Visit (Visit 1). Participants using ocular hypotensive medications who did not have prior documentation of unmedicated IOP ≤ 21 mm Hg were instructed to undergo a minimum 30-day washout period, then to return (Visit 1a) for an unmedicated IOP measurement to determine if they met the IOP eligibility requirement. Ocular hypotensive medications could be resumed after this assessment.

Participants who met study eligibility requirements after Visit 1/1a were provided with an OPAP kit containing goggles, pump (programmed to apply -5 mm Hg NP to each eye, for a maximum of 8 hours' nightly use), and accessories for at-home use. After training on use of the OPAP by qualified investigational site staff, participants were instructed to begin with 30 minutes of wear during waking hours, then increase wear time by 30 minutes on each subsequent day over the following 7 days; device use during sleep was not mandated during the first 7 days of this "run-

in" phase. Participants were then scheduled to return for Visit 2 (Day -7). At Visit 2, adverse event assessment and slit-lamp biomicroscopy were performed, OPAP usage data was downloaded, and the pump was re-programmed to apply increased NP (approximately 50% of the baseline IOP measured that day) for a treatment period of 8 hours in both eyes. **Figure 13** depicts the recommended re-programming of negative pressure. Participants were instructed to use their goggles each night during the following 7 days.

At Visit 3 (Day 0) participants were evaluated for the ability to successfully use the OPAP during ≥ 3 hours of sleep on at least 3 of the previous 7 nights. Participants who did not meet this criterion were exited from the trial. Those who met this criterion remained eligible to proceed onto randomization. One eye was randomly assigned to receive NP application while the contralateral eye was assigned to receive no NP application.

At this visit, NP was programmed for the study eye by determining the difference between the baseline IOP measured in-clinic that day and a reference IOP of 6 mm Hg. Therefore, Programmed NP = Measured IOP – 6mmHg. The NP for the control eye was programmed for no negative pressure.

> ***FDA Comment:*** *Note that investigators were allowed to adjust the NP setting on the study eye for subsequent home use per his or her discretion. See further discussion in* ***Section 6.3****.*

Subjects were asked to use the OPAP during sleeping hours for approximately 6 hours/night at least 5 nights/week. They were also scheduled to report for an overnight session in a sleep lab within the following 21 days to measure nighttime IOP during use of the OPAP. This sleep lab visit (Visit 3a) was 8 hours in duration (10 pm to 6 am). For the sleep lab visit, the baseline supine IOP in each eye was measured prior to placement of the OPAP goggles. The participant then put on excursion goggles and IOP was again measured before initiation of NP via Excursion pneumotonometry. Participants then switched to using the OPAP goggles and the negative pressure (while sleeping and/or resting supine) setting programmed from Visit 3 (Day 0). At approximately 11 pm, 2 am, and 5 am, subjects exchanged their OPAP goggles for Excursion goggles (a version of the OPAP goggles customized to allow IOP measurement during wear), and IOP during NP application was measured with the subject in supine position in both eyes. Following the sleep lab session, the OPAP was re-programmed for home use based on the baseline IOP from the sleep lab in the supine position.

Participants continued to wear the goggles at their habitual NP and were asked to return for 5 in-office assessments at approximately 6, 12, 26, 38, and 52 weeks (Visits 4-8) after randomization. At each in-office follow-up visit, IOP was measured, at-home OPAP usage data was downloaded, and safety assessments were performed. Investigators at each site were given discretion to modify the NP setting of the study eye for at-home use based on data obtained from the device and subject feedback (for safety, however, the NP could not be programmed to a reference IOP < 6 mmHg).

At Visit 3 (Day 0), Visit 6 (Week 26), and Visit 8 (Week 52), baseline IOP was measured in clinic, then participants donned the Excursion goggles programmed with their habitual NP for the study eye (no NP for contralateral eye), and IOP was measured in both eyes afterward.

Just prior to the Week 52 in-office visit, participants repeated the sleep lab using the same methodology as described for the initial sleep lab.

The schedule can be summarized as follows:

- Visit 1 (Day -14) – Baseline Visit 1, includes informed consent form and screening for inclusion/exclusion in the study prior to introductory period of home-use
- Visit 1a (30 + 7 Days after Visit 1) – Optional Baseline Visit, if needed, to obtain unmedicated IOP following ocular, hypotensive medication washout OU
- Visit 2 (Day -7, ± 1 day) – includes follow-up to address any home-use issues and assessment of wear time (data downloaded from pump) following first week of MPD use
- Visit 3 (Day 0, - 3 to + 7 days for sleep trial and +21 days for sleep lab) – includes randomization on Day 0 if minimum sleep wear threshold is achieved during prior 2-week run-in period, and supine IOP measurements in sleep lab within 21 days following randomization.
- Visit 4 (Week 6 ± 14 days)
- Visit 5 (Week 12 ± 14 days)
- Visit 6 (Week 26 ± 28 days)
- Visit 7 (Week 38 ± 28 days)
- Visit 8 (Week 52 ± 28 days) includes supine IOP measurements in sleep lab
    - Sleep Lab session must precede the in-clinic visit at Week 52 (Visit 8) to facilitate study exit.

A comprehensive schedule of study treatments and clinical assessments at each in-clinic and sleep lab visit can be found in **Table 16.**

6.3 Selection of Treatment Doses in the Study

The parameters used for OPAP pump programming for in-clinic IOP measurement during NP application and subsequent home use are summarized in **Table 17**. The typical IOP-lowering response during use of the OPAP is approximately 40-60% of the applied NP.

While programming was intended to remain constant over the course of the study, investigators were given discretion (Revision 5 of the protocol) to adjust the study eye NP setting for each subsequent home use period based on data from device home use and participant comfort. For safety purposes, however, the program could not target a reference IOP < 6 mmHg. In total, NP programming for home use was adjusted for 15 participants; for 8 participants, adjustments were based on the occurrence of 1 or more AEs (e.g., mild to moderate lid edema, periorbital edema, lid erythema, headache, or ocular pain).

FDA Commentary: *Given that investigators were able to adjust the NP per their "discretion", it appears that the manner in which investigators programmed the NP setting is unstandardized for the majority of the duration of the trial. Furthermore, there is no instruction in the sponsor's draft labeling on how physicians should "dose" the NP setting and wear time.*

In Deficiency 2.b of the ***AINN deficiency letter*** *dated November 8, 2023, it was noted that some AEs were reported after an increase in NP level, but it was unclear how discretionary changes to NP level and AE occurrence were related, and how investigators deviated from the pre-specified "dosing" nomogram. In the January 3 response (DENXXXXX2/SXX1, Page 26), the sponsor provided line data on each ocular and periorbital AE reported post-randomization with the NP setting on the date of randomization and any subsequent adjustments made for the duration of the participants' trial participation. In addition, the sponsor stated, "The evaluation of temporal relationships between onset of device-related AEs and NP settings is complicated by the fact that many of the periorbital or lid edema and periorbital or eye pain events were patient-reported, transient, and intermittent, with no evidence of the event present during ophthalmic examination at the subject's clinic visit. Also, subjects were not always precise about onset, frequency, or duration of these events. Onset of periorbital or lid edema and periorbital or eye pain was reported with the Day 0 in-clinic NP setting for 13 subjects. Eleven (11) additional subjects reported onset of these types of AEs after a subsequent NP adjustment based on a higher sleep lab supine mean IOP than previously referenced. The periorbital or lid edema and periorbital or eye pain AEs were reported with NP settings ranging from -6 to -19 mmHg. There was no difference in the number of subjects who received a downward adjustment in NP in response to the AE(s) vs. those who continued with the setting as programmed (n=9 subjects in each category). Six (6) subjects who experienced these AEs withdrew from the study."*

Please note that Listing 2-1 provides information on 37 participants. The sponsor did not provide a tally of the number of participants in this table whose NP levels were increased between Day 0 and the initial sleep lab visit and at other time points throughout the post-randomization period of the trial. In addition, no information was provided on the reason for increase (for example, whether it was due to investigator discretion alone, or due to increase in the supine sleep lab pre-NP IOP compared to the Day 0 pre-NP IOP).

6.4 Analysis Populations

The following populations were defined by the sponsor:

Intent-to-treat (ITT)	All randomized participants.
Safety	All randomized participants who had "at least one application (of any duration) of NP **after** randomization

Modified intent-to-treat (mITT)	All randomized participants who had "at least one full application of NP (defined as a minimum of 20 minutes of NP in the home use setting) to the study eye after randomization (between Visit 3 and Visit 8)"
Per-protocol (PP)	All participants in the mITT population "who met all eligibility criteria, had no major protocol deviations, and completed their Week 52 sleep clinic and in-office visits."

Table 18 presents the number of subjects in each defined analysis population (Vol. VII, p. 158).

FDA Commentary:

The number of participants in the ITT, Safety, mITT and PP populations were 94, 93, 93 and 60, respectively.

Based upon the definitions provided for the safety populations, the safety events that occurred during the run-in phase of the trial were not included. The sponsor was asked interactively to provide safety information related to the run-in period on September 28, 2023. The sponsor provided the relevant safety information in summary format on October 2, 2023.

7. Clinical Trial Results

7.1 Accountability

165 participants were enrolled. 55 were found ineligible or otherwise withdrew consent by the baseline or washout visit. 110 participants entered the "run-in" phase and returned for the Day -7 visit (Visit 2). During the "run-in" phase, eight participants discontinued: four withdrew consent at Visit 2 and four discontinued due to concerns with sleep-lab availability during the COVID-19 pandemic. 106 returned for the Day 0 visit (Visit 3). Another eight participants were discontinued due to ineligibility or withdrawal of consent. Therefore, 93 participants were randomized at Day 0 (Visit 3). 31 randomized participants (33%) failed to complete both the final sleep lab and the Week 52 in-office visit and two were reported with major protocol deviations; thus, a total of 62 participants (64.5%) completed the trial. Of these 31, "almost half…terminated study participation within 12 weeks after randomization and 25 (80.6%) had discontinued by Week 26". The sponsor provides the following explanations for these 31 participants:

- 20 participants discontinued early by withdrawing consent. Of these, five had experienced mild device-related AEs within the previous month that resolved prior to discontinuation.

- Two participants had moderate to severe COVID-19 during their study participation.
- Five were discontinued due to non-compliance with device use requirements.
- Two participants experienced periorbital contact dermatitis OU, which the investigator felt may be a reaction to the OPAP goggles.
- Two participants were discontinued due to closure of a study site.
- One participant was diagnosed with Stage IV pancreatic cancer and entered hospice.
- One participant was lost to follow-up.

Table 19 describes the subject accountability for the mITT Population. Three participants who missed the initial sleep lab due to COVID-related concerns were in the PP population ((b)(6) (b)(6), and (b)(6) .

FDA Commentary: *It is important to note that* ***Table 19*** *only depicts those who had at least one full application of negative pressure. Footnote 1 of* ***Table 19*** *states:*

> *"The mITT Population consists of all randomized subjects who had at least one full application (minimum of 20 minutes in home use setting) of NP to the study eye between Visit 3 and Visit 8. All but 1 of the 94 subjects randomized received at least one full NP application; therefore, the mITT population consisted of 93 subjects (1 subject, after randomization on Day 0, had GAT IOP measurement > 21 mmHg and was discontinued prior to NP application)."*

The sponsor was asked interactively to provide clarification regarding the one participant that was excluded after randomization and on the participants who could not meet "minimum" sleep-wear requirements by the end of the "run-in" phase. On October 2, 2023, the sponsor clarified that this participant ((b)(6)) "had a documented history of unmedicated IOP > 21 mmHg, which was not identified by site personnel until after Visit 2 (Day -7)." Seven participants were unable to achieve the minimum-required sleep-wear requirements (average of ≥3 hours of sleep wear during at least three nights of the consecutive 7-day period leading up to Day 0. Of these seven, two (b)(6) and (b)(6)) had devices that had been "overprogrammed."

7.2 Demographics and Baseline Characteristics

For the mITT population, the mean age was 62.4±10.7 years. 67.7% were women. Of the 93 subjects, the majority (n=64, 68.8%) were white, 13 (14.0%) were Black/African American, and 15 (16.1%) were Asian. Most subjects (n=75 or 80.6%) reported Ethnicity of not Hispanic/not Latino. The demographics for the mITT population and PP population can be found in **Table 20** and **21**, respectively.

For the mITT population, mean study-eye baseline IOP by GAT was 14.7±2.0 mm Hg (range 12 – 20 mm Hg) and the mean study-eye baseline visual field (VF) mean deviation (MD) was -4.03±4.86 dB (range -22.59 to +2.38 dB). Most participants were on either no (41/93; 44.1%) or

only one (35/93; 37.6%) IOP-lowering medication at the time of screening. The median study-eye vertical cup-to-disc (C/D) ratio was 0.7 (range 0.3 to 0.95). The mean study-eye central corneal thickness (CCT) was 536.2±38.2 µm (range 413-640 µm). **Table 22** summarizes the baseline characteristics for the mITT population, assessed at Visit 1 (Day -14).

***FDA Commentary**: These demographics are roughly similar between the PP and mITT populations, although the proportion of Asian participants decreased in the PP population. The history of any prior IOP-lowering procedures was not reported for the cohort.*

The Panel is encouraged to consider the demographics and baseline characteristics of the population of the clinical trial as it pertains to the population in the proposed IFU (i.e., adult patients with OAG and IOP ≤ 21 mmHg).

*In Deficiency 2.d of the **AINN deficiency letter** dated November 8, 2023, FDA reiterated concerns previously conveyed written feedback for QXXXXX4) regarding harmful effects from device use in individuals who are either more "rapid [glaucoma] progressors" or who have advanced glaucoma. Clarification was requested on whether "rapid progressors" were specifically targeted in the CP-X19 and CP-X10 trials and on how many of the CP-X19 cohort were considered to have advanced glaucoma. In the January 3, 2023, response (Page 29, DENXXXXX2/SXX1), the sponsor stated, "'Rapid progressors' were not prospectively identified in either CP-X10 or CP-X19. Additionally, as the CP-X10 study had a follow-up duration of only 90 days, it is doubtful rapid progressors would have been identified post-hoc. The definition of 'rapid progressors' is also not consistently defined in the literature." The sponsor also stated that 31 randomized participants had advanced glaucoma as defined by "a baseline C:D ≥0.8." 11 of these 31 "discontinued participation prior to study completion (all but 1 discontinued within approximately the first 4 months). Device-related AEs within this cohort were similar in type and severity to those reported in the overall study population." "No subject experienced > 1 line change in distance visual acuity in the study eye during the course of their study participation. Post-hoc masked review of Week 52 visual field and OCT images by the visual field reading center showed no evidence of progression in the study eye of any of these subjects."*

In DENXXXXX2, the Sponsor stated that PP analysis population had 60 participants. However, at the 52-week measurement, 33 participants were considering "missing". The demographics information for the PP "completed" subjects (N=60) vs missing subjects (N=33) was not presented. Therefore, this information was requested in DENXXXXX2/SXX1 (deficiency 8). The Sponsor provided the mean age for the "completed group" (61.4 years old) and the mean age for the "missing group" (64.2 years old). The "missing" group comprised a higher percentage of females (72.7%=24/33 vs. 65.0%=39/60 in the "completed" group) and a higher percentage of Asian subjects (24.2%=8/33 vs. 11.7%=7/60 in the "completed" group). Additionally, the study eye assignment in the "missing group" was more frequently OS (57.6%=19/33 vs. 46.7%=28/60 in the "completed" group).

7.3 Protocol Deviations

Protocol deviations are summarized in **Table 23**. Three major protocol deviations were reported; two involving "incomplete excursion tonometry at the Week 52 sleep clinic [visit]," and the other involving "a brief exposure of the control eye to NP after randomization." 124 minor protocol deviations were reported. The sponsor states that no Adverse Events (AEs) were associated with the protocol deviations involving incorrect NP programming. There were 13 missed assessments (minor protocol deviation). For clarification, none of the 13 missed visits were the Week 52 in-office or sleep lab visits.

FDA Commentary: *The number of participants involved in each category of deviation was not specified, therefore, it was unclear whether participants may have been attributed to more than one type of deviation. The sponsor also did not specify what the "missed assessments" were. On October 2, 2023, the sponsor provided two tables to clarify these concerns (**Tables 24 and 25**).*

From these tables, the following information was concluded:

- *13 "missed assessments" involved 11 participants.*
  - *In four cases, BCDVA was not performed "when corrected distance [VA] (CDVA) was measured ≥10 letters worse than Baseline. An adverse event for BCDVA worsening was reported for 1 of these subjects* (b)(6) *whose vision fluctuated between 20/20 and 20/32 throughout the study; in the remaining 3 subjects, CDVA was similar to Baseline at subsequent visits."*
  - *There were three cases of "missed collection of [OCT] imaging to complement visual field testing."*
  - *In one case, "a slit lamp examination was not performed on Day -7."*
  - *There were five cases involving "the lack of IOP and/or Excursion Testing, with one case (Subject* (b)(6) *related to the primary effectiveness variable – masked IOP and Excursion Testing at Week 52; this deviation was considered to be 'major' in nature."*
- *The seven instances of "incorrect [NP] programming" post-randomization occurred in four participants.*
  - *The sponsor provided the following information in relation to the participants that had incorrect NP programming: "Incorrect programming occurred at the Day 0 Visit, affecting both in-clinic Excursion testing and home-use thereafter for 2 subjects (*(b)(6) *and* (b)(6)*), while incorrect programming affected Subjects* (b)(6) *and* (b)(6) *at their initial sleep lab and Subject* (b)(6) *at the Week 26 sleep lab (Note: The Week 26 sleep lab requirement was removed in Revision 6 of the study protocol). Within this group, three participants completed Week 52 Visit requirements, while one participant* (b)(6) *was discontinued for study non-compliance approximately 4 months after study randomization."*

7.4 Pump Programming and Home Use

The NP programmed for study and control eyes at each in-clinic visit after randomization for the mITT population is summarized in **Table 26**; this setting was used during the home use period following the respective in-clinic visit. Of note, the Week 38 program was intended for the wear period from Week 38 until the final scheduled visit at Week 52.

The mean programmed NP over the scheduled study visits ranged between -10.0 mmHg (Day 0) to -12.1 mmHg (Week 12) (**Table 26**). At Day 0 (Visit 3), the NP programming was based on the Visit 3 in-clinic IOP measured with the participant seated prior to donning excursion goggles. The "habitual" NP programming used at subsequent visits was based on the initial sleep lab (Visit 3a) IOP measurements prior to donning goggles with the participant in supine position. Because the habitual NP was intended to be the same throughout the remainder of the trial, the habitual NP was used for the final sleep lab and the Week 52 in-clinic assessments.

***FDA Commentary**: Please note that a number of minor protocol deviations were reported on "under-" or "over-programming." However, due to insufficient detail provided related to the protocol deviations, the extent of this deviation in programming is unclear.*

*In Deficiency 3.b of the **AINN deficiency letter** dated November 8, 2023, it was noted that the manner in which investigators programmed the NP setting was unstandardized for the majority of the duration of the CP-X19 trial. Deficiency 3.b also noted that investigators were instructed to adjust NP level if the initial sleep lab-derived, nocturnal supine baseline IOP was different than the in-office baseline IOP, but the current labeling does not instruct the prescribing physician to obtain supine IOPs in the overnight hours to establish the "baseline" IOP on which programming will be based. The sponsor has not specified whether future end-users are to program the device in the same way. Additional information was requested clarifying how NP programming was set and adjusted throughout the trial.*

*In response (DENXXXXX2/SXX1), the sponsor clarified that investigators were allowed discretion to adjust NP level based on participant complaints, AEs, or decreased sleep wear time. Of the 93 participants randomized, home-use NP level was adjusted based on initial sleep lab IOP for 59 (63.4%). "Additional adjustments (both increasing and reducing NP) were made for the study eye of 45 subjects based on patient comfort, wear time, adverse events and, in some cases, the desire to increase IOP reduction. Of the 45 subjects for which a NP adjustment was made, 25 reported no device-related adverse events." 53 participants were programed for NP application at > -12 mm Hg "at some point during the" trial, and of these 53, 38 (71.7%) completed the trial while 15 (28.3%) exited early. Refer to **Tables 28 and 29** for information (study ID, NP levels on Day 0 and after initial sleep lab visit, wear time, whether device-related AE was reported) on these 53 participants.*

***FDA Commentary Cont'd**: The sponsor also revised the physician labeling (i.e., Instructions for Use) to provide NP programming instructions based on data generated within the CP-X19 trial (**Attachment 3**).*

*The Agency also raised concerns regarding the maximum duration of 12 hours of nightly use and the max allowable programable applied NP (-20 mmHg) per the device labeling and whether the data collected during their CP-X19 trial supported this labeled use. See **Section 7.5.1** below for additional discussions regarding this issue.*

7.5 Safety Outcomes

7.5.1 Adherence to OPAP Home and Sleep Lab Use

7.5.1.1 OPAP Home Use

In DENXXXXX2, the device is labeled to be programmable for up to a maximum of 12 hours of use, at up to a maximum of -20 mm Hg of applied NP. The sponsor states in the "Physicians Application Quick Start Guide" that the "factory default" wear time is 8 hours.

Device wear time was documented based on use data recorded by the device. "Between Day 0 and Week 6, subjects used the OPAP on approximately 87% of available days." In this interim period, the mean wear time was 5.5±1.22 hours/day. The sponsor noted (Volume VII, page 63) that "The mean number of days on which the OPAP was used between visits gradually decreased over the course of the study; however, subjects used the OPAP on 78% or more of the days between each in-office examination, which translates to an average of more than 5 days/week." "Of note, while the OPAP was programmed or a maximum of 8 hours' use, the system did not prevent subjects from restarting treatment after an 8-hour treatment cycle is completed."

Descriptive statistics of mean device wear time during the CP-X19 trial are shown in **Table 30**. Note that these are stratified by trial intervals (Week 0 – 6, 6 – 12, 12 – 26, 26 – 38, and 38 – 52).

7.5.1.2 OPAP Sleep Lab Use

At the initial sleep lab visit, mean IOP prior to NP application was > 2 mm Hg higher than the corresponding Day 0 in-clinic IOP for 66.3% of study eyes (n=53) and 43.8% of control eyes (n=35). For 32.5% of study eyes (n=26) and 48.8% of control eyes (n=39), mean sleep lab IOP was within ± 2 mm Hg of the corresponding Day 0 visit (in the majority of cases, sleep lab IOP was slightly higher than that measured on Day 0), and mean sleep lab IOP was > 2 mm Hg lower

than the corresponding Day 0 visit for only 1 study eye and 6 control eyes. At the final sleep lab visit, mean IOP was > 2 mm Hg higher than the corresponding Week 52 in-clinic IOP for 55.7% of study eyes (n=34) and 49.2% of control eyes (n=30). For 36.1% of study eyes (n=22) and 43.3% of control eyes (n=27), mean sleep lab IOP was within ± 2 mmHg of the corresponding Week 52 visit. Similar to the initial sleep lab visit, the majority of eyes had sleep lab IOP higher than that measured at the Week 52 in-clinic visit. Mean sleep lab IOP was > 2 mm Hg lower than the corresponding Week 52 visit for 5 study eyes and 4 control eyes. Please refer to **Table 31**.

At the initial sleep lab visit, 33 of 160 eyes had IOP > 21 mmHg before NP application at 11:00 pm. This number increased to 42 at 2:00 am, and to 45 at 5:00 am. Of the 122 eyes for which IOP was measured at the final sleep lab, 29, 40, and 42 had IOP > 21 mmHg prior to NP application at the same time points, respectively. During NP application, IOP was > 21 mmHg for the study eye of only a single subject (b)(6) at only 1 timepoint (5:00 am at the final sleep lab). At this visit, the subject's study eye NP setting was -7 mmHg and pre-NP IOP was 22.5 mmHg at 11:00 pm, 23.1 mmHg at 2:00 am, and 25.8 mmHg at 5:00 am; IOP measurements during NP application were 15.3 mmHg, 16.8 mmHg, and 22.5 mmHg at these same timepoints, respectively. No adverse events were reported for this subject.

FDA Commentary: *FDA requested (deficiencies 3.a.i, 3.a.ii, and 3.a.iii of the* ***AINN deficiency letter*** *dated November 8, 2023) descriptive statistics on the device wear time during the two sleep lab visits and information on how nocturnal, supine IOP prior to NP application compared to the in-office pre-NP IOPs collected, and clarification on how many of the three sleep-lab IOP checks had been performed out-of-window.*

Details regarding the sleep lab visits summarized above were provided in response to deficiency 3.a.ii. Note that descriptive statistics of the IOP rise (or decrease) were not provided. Additionally, stratified tallies within the category of ">2 mm Hg higher" than in-clinic Day 0 IOP (e.g., those with >3 mm Hg rise, >4 mm Hg rise, etc.) were not provided.

The sponsor also clarified (in response to deficiency 3.a.iii) that the assessment of change in sleep-lab IOP was performed by averaging two measurements (while the participant is wearing the OPAP goggles before and during NP application). If the two measurements differed by more than 2 mm Hg, a third measurement was taken and the median of the three measurements was used. At the Week-52 sleep lab visit, IOP measurements were within window at all three measurement time points for 59 of the 62 participants. The distributions of the assessment times within-window are shown as histograms stratified by the Week-26 vs. Week-52 sleep lab time points; please refer to Figures 1, 2, and 3 from DENXXXXX2/SXX1, p. 35-36.

FDA Commentary Cont'd: *FDA raised concerns that given the mean wear time was below the maximum programmable labeled use of 12 hours that the safety results did not reflect the labeled intended use of the device and that given that very few participants could achieve the "factory default" wear time of 8 hours raises concerns regarding the tolerability of the use of the device. In response to Deficiency 2.c of the* ***AINN deficiency letter*** *dated November 8, 2023, the sponsor provided additional information related to the concern regarding the inability of CP-X19 participants to achieve the full, recommended 8 hours' device wear time was requested. Mean wear time categorized by ≤4 hours, >4 hours, >6 hours, and >8 hours across the five trial intervals are shown in* ***Table 32****. Additional information was provided indicating that eight of 93 participants (8.6%) used the device with NP levels of -17 to -20 mm Hg "for at least 26 weeks during the" trial (Page 27, DENXXXXX2/SXX1). Three of these eight (37.5%) were reported with device-related AEs (*(b)(6)*: mild periorbital edema;* (b)(6)*: mild periorbital edema, mild symptoms and signs of dry eye;* (b)(6)*: mild periorbital edema). The mean wear time for these eight participants are shown in* ***Table 33****. FDA's perspective isthat eight randomized participants using the highest range of allowable NP level may limit the ability to make any conclusions regarding the safety profile of the device at the highest NP levels allowable on the device.*

In addition, the sponsor provided the wear time during the sleep lab visits in the response to Deficiencies 2.c and 3.a.i. During sleep lab visits, after the initial 11:00 pm (± 60 minutes) IOP measurements, participants were required to wear the OPAP until 5:00 am (± 60 minutes), with a brief interruption for excursion IOP measurements at 2:00 am. At the initial sleep lab visit, the mean wear time was 2.9 ± 0.3 hours between 11:00 pm and 2:00 pm and 2.8 ± 0.5 hours between 2:00 am and 5:00 am. At the Week 52 sleep lab visit, mean wear time was 2.9 ± 0.3 hours between 11:00 pm and 2:00 pm, and 2.6 ± 0.5 hours between 2:00 am and 5:00 am. Please refer to ***Table 34****.*

As part of the response to Deficiency 2.c, the sponsor stated (Page 28, DENXXXXX2/SXX1)that device labeling (i.e., physician Instructions for Use, patient Instructions for Use) were "revised for consistency with data provided from the CP-X19 study and cautionary statements have been added regarding maximum wear time and maximum NP setting programming." It should be noted that on page 10 of the physician Instructions for Use, the sponsor stated that "treatment duration can range from 1 to 8 hours." The allowable range of NP level remains unchanged at -5 to -20 mm Hg.

The Panel will be asked whether the available data supports the proposed programmable NP range of -5 to -20 mmHg and proposed range of wear time of 1 to 8 hours.

***FDA Commentary**: In the FDA feedback sent to the sponsor on April 29, 2022 for QXXXXX4, the Agency expressed safety concerns related to the tolerability of the device as the previously collected clinical (including the living donor, laser speckle flowgraphy, and OCT/OCT angiography studies) and non-clinical (i.e., cadaver) data do not adequately reflect characterization of how the device performs 1) for the labeled use of up to 8 hours nightly and 2) for long-term device use. The new data the sponsor had proposed in QXXXXX4/SXX1 to collect to support a future De Novo also did not address these concerns. It was noted that all the SGEs echoed this concern.*

*Additionally, in the **decline letter** dated September 10, 2021, for DENXXXXX1/S002, FDA communicated concerns (deficiency (2a)) that, for the majority of the CP-X10 trial duration, no participant achieved an average daily wear time of the full 8 hours as required and that this suggests that, for the majority of participants, adherence to the recommended wear time may not be very "well-tolerated." There is a concern that suboptimal adherence confounds the characterization of safety, which may underestimate the rates of adverse events (AEs) reported in CP-X10. Concerns regarding characterization of long-term device was also raised as that trial was designed to only last 90 days.*

*FDA requested in Deficiency 4.c of the **AINN deficiency letter** dated November 8, 2023, that the sponsor provide any additional information on health-related quality-of-life (HRQOL) metrics available to further characterize the use of the device. In response (DENXXXXX2/SXX1), the sponsor stated that HRQOL data were collected only in the CP-X10 trial; that is, there were no HRQOL data collected in the CP-X19 trial. This data the sponsor refers to are responses from CP-X10 participants on the SHPC-18 (Symptoms and Health Problem Checklist) questionnaire, a shortened version of a longer, 43-item questionnaire originally used in the Collaborative Initial Glaucoma Treatment Study (CIGTS). Items cover eye symptoms and visual function symptoms. Summary responses on the SHPC-18 from CP-X10 are summarized in **Section 4.3**. Please note that there may be uncertainty with the interpretation of individual item scores on the SHPC-18 (e.g., whether a 1- or 2-point change in a score is clinically meaningful, and what reported symptoms can be attributed to, as this may be confounded by concomitant use of medications). The only other clinical trial in which patient questionnaires were administered was in Protocol CP-X22 (see discussion in **Section 8**).*

7.5.2 Adverse Events (AEs)/ Complications

7.5.2.1 Ocular Adverse Events

Ocular AEs for the safety population are summarized in **Table 35**. A total of 39 ocular AEs were reported in 25 study eyes and 17 ocular AEs were reported in 13 control eyes. The most frequently occurring AEs in study eyes were lid edema (11 eyes; 11.8%), mild signs and symptoms of dry eye (5 eyes; 5.4%), mild to moderate conjunctival hyperemia (4 eyes; 4.3%),

and mild to moderate eye pain (3 eyes; 3.2%). The following participants experienced notable adverse events:

- Participant (b)(6) reported severe lid edema in the study eye approximately 4 months after randomization (NP programmed to -14 mmHg) and discontinued device use temporarily. The AE was considered resolved 8 days later. Upon resumption of device use, moderate lid edema was observed, and device use was again discontinued; lid appearance returned to baseline within the following week. This participant terminated study participation prior to the Week 26 Visit following the occurrence of multiple AEs (mild periorbital contact dermatitis OU, mild visual disturbance in the absence of BCDVA change in the study eye, and moderate abrasion on the left side of the nose), all of which resolved without sequelae.

- Participant (b)(6) experienced moderate (3+) lid edema in the study eye after completing the initial study sleep lab where the NP application was increased from the Day 0 Visit setting of -12 mmHg to -14 mmHg based on the subject's sleep lab baseline supine IOP. The participant discontinued device use for 28 days, then resumed treatment with NP adjusted to -12 mmHg. At the Week 12 visit, lid edema had resolved, and ocular health was otherwise unremarkable. This subject completed 52 weeks of device use without further complication.

Transient eye pain believed to be related to "NP settings during device wear" was reported in three study eyes (b)(6) . Participant (b)(6) reported mild, intermittent eye pain starting about one hour into each device wear period and modified the device-wear schedule to approximately three hours nightly for the duration of the trial. Pain resolved with discontinuation of device use after completion of the trial. Participants (b)(6) and (b)(6) reported moderate eye pain that resolved within four days of "palliative treatment and reduction in the NP setting."

Loss of best-corrected distance visual acuity (BCDVA) ≥10 letters from baseline was reported in two study eyes (b)(6) and in two control eyes of different subjects.

For (b)(6), BCDVA in the study eye was 55 total letters read (TLR) at baseline and 45 TLR at Week 6; 1+ anterior basement membrane dystrophy (ABMD) in both eyes was noted on Day 0 slit-lamp biomicroscopy. The study eye BCDVA subsequently fluctuated "between 20/25 and 20/32" during the trial. BCDVA in the study eye was 20/40 at the Week 52 visit. At a visit three weeks after the final visit, BCDVA was 20/25.

(b)(6) was reported with a change in TLR from 49 at Day -14 to 14 at Week 26. 1+ SPK and 1+ ABMD was noted in both eyes at Week 26. Three days after the Week-26 sleep lab visit, a moderate epithelial defect was reported for (b)(6) in the study eye due to sleep lab excursion tonometry; BCDVA in the study eye was 20/100. The epithelial defect was treated and was reported as resolved four days later. BCDVA was 40 TLR at Week 38 and 50 TLR at Week 52.

***FDA Commentary**: Additional details regarding loss of BCDVA, as summarized above, was provided in Attachment CP-X19 in the sponsor's DENXXXXX2/SXX1 response (**Attachment 2** of executive summary).*

7.5.2.2 Periorbital Adverse Events

Periorbital AEs are summarized in **Table 36.** 20 AEs were reported for 17 study eyes and seven AEs were reported for seven control eyes. The sponsor states that all periorbital AEs resolved prior to participant study completion or discontinuation. The most frequently reported periorbital AEs in study eyes were mild to moderate periorbital edema (12 eyes; 12.9%) and mild periorbital contact dermatitis (4 eyes; 4.3%). The sponsor concludes that all cases of periorbital contact dermatitis were mild in nature, resolving with over-the-counter medication.

- Out of the 12 periorbital edema cases, two (participants (b)(6) were reported as "moderate" in severity.
    - Moderate left-sided periorbital edema (left eye was the study eye), periorbital pain, and headache started in (b)(6) were reported four days after the first sleep lab visit. These symptoms lasted approximately 8 to 10 hours after stopping device use. NP level had been increased to -16 mm Hg (based on the supine sleep-lab baseline IOP) from the originally-programmed NP level of -10 mm Hg (set at Day 0). The AE was downgraded to mild after NP was adjusted to -10 mmHg and a recommended 3-day break from device use. The edema, pain, and headache resolved within the following week. The NP level remained at -10 mm Hg for the remainder of the trial. Participant (b)(6) completed the 52-week trial.
    - Moderate left-sided periorbital edema (study eye was the left eye) was also reported for participant (b)(6) at the Week 6 visit. The programmed NP level at the time of randomization was -6 mm Hg. (b)(6) was advised to discontinue device use for three days, then resume, starting with approximately 3 hours' nightly use and then gradually ramping up wear time. The AE resolved by the Week 12 Visit; average nightly wear time was 4.2 hours. This participant withdrew consent approximately eight weeks later and exited the trial shortly after.
- There were two reported "periorbital pain" cases (participants (b)(6) and (b)(6)). .
    - Participant (b)(6) is discussed above.
    - Participant (b)(6) reported mild periorbital pain around both eyes (study eye was the left eye) that had started the night after randomization (Day 0). Programmed NP level was -8 mm Hg. At an unscheduled visit one week after Day 0, BCDVA was reported as 20/25 in the study eye (same as the baseline BCDVA) and the

ocular examination was unremarkable. (b)(6) elected to withdraw consent at that visit.

- There were four participants (b)(6) who "experienced one or more ocular or periorbital AEs with onset during the device use run-in period prior to randomization that were considered to be possibly, probably, or definitely device-related."

    - (b)(6) (study eye: left eye) was reported with myokymia of the left lower lid that had started two days before the Day 0 visit. NP level was programmed at -10 mm Hg at Day 0. Other AEs reported for (b)(6) were intermittent conjunctival hyperemia and lid edema that persisted for approximately three hours after goggles removal; 2+ lid edema was noted at the Week-26, Week-38, and Week-52 visits. A red rash on the upper left cheek that was reported three days after NP level was increased to -13 mm Hg.

    - (b)(6) (study eye: left eye) reported periorbital edema in both eyes (2+ right/control eye, 1+ study eye) that had started after the Day -7 visit. At randomization, NP level was set at -8 mm Hg, and increased to -15 mm Hg after the initial sleep lab visit. At the Week-12 visit, (b)(6) reported mild, intermittent eye pain in the study eye about one hour after initiating device use, starting after the post-sleep lab NP level increase; NP level was decreased to -12 mm Hg, but the eye pain continued. After the Week-26 sleep lab visit, NP was increased again to -16 mm Hg, then decreased to -14 mm Hg one day later. (b)(6) completed the Week-52 visit, and reported his eye pain resolved the day after discontinuation of device use.

    - Participant (b)(6) (study eye: left eye) presented with a moderate abrasion on the upper part of the nose (adjacent to where the nose bridge is positioned during device use) at the Day -7 visit. Dry skin around both eyes two days prior to Day -7 was also reported. These AEs were thought to be caused by friction from the goggles. The nasal abrasion resolved 10 days later. Bilateral periorbital contact dermatitis was reported with onset of 10 days prior to randomization. At randomization, NP level was programmed at -9 mm Hg. This was increased to -14 mm Hg after the initial sleep lab visit. (b)(6) reported 1+ bilateral eyelid edema approximately seven months after Day 0 and NP level was decreased to -10 mm Hg. (b)(6) exited the trial approximately six weeks after the Week-38 visit due to a diagnosis of Stage IV pancreatic cancer.

FDA Commentary: *Additional details regarding the periorbital adverse event cases, as summarized above, were provided in DENXXXXX2/SXX1 (**Attachment 2**).*

7.5.2.3 Non-Ocular AEs

24 non-ocular AEs were reported for 12 participants (12.9%). Two participants (b)(6) experienced non-ocular AEs ("mild to moderate" headaches during device use) that were considered "to be possibly, probably, or definitely device-related." The two AEs are described as follows:

- Participant (b)(6), previously discussed above, reported onset of moderate headache after the initial sleep lab visit when NP settings had been increased based on the sleep lab baseline IOP. Headache resolved within the following week and additional AEs were reported for this participant as discussed above.

- Participant (b)(6), previously discussed above, reported onset of moderate headaches, mild lid erythema, and mild periorbital edema starting approximately 12 days prior to Day 0. Headaches were described as transient and intermittent, associated with device use and localized to the study eye eyebrow area. The NP level was reduced from -14 mm Hg to -11 mm Hg for approximately 1 month, then followed with weekly increases of 1 mmHg to return to the original setting by Week 6. The AE resolved by the Week 6 Visit and did not recur during the remainder of the 52-week study period. (b)(6) continued to have intermittent, transient eyelid erythema and periorbital edema throughout the duration of the trial that resolved upon discontinuation of device use the night before the final visit.

***FDA Commentary**: Note that the AEs tallied in the sections above do not include the AEs reported during the 14 day "run-in" phase of the CP-X19 trial. FDA requested this information in our **AINN deficiency letter** dated November 8, 2023 (deficiency 2.a). CP-X19*

*In the sponsor's response (DENXXXXX2/SXX1) they state that of the 122 participants who started the "run-in" phase, a total of 15 AEs (two ocular, seven periorbital, six non-ocular) were reported for nine participants (7.4%). The ocular AEs were meibomian gland dysfunction and eyelid myokymia. The periorbital AEs were nasal abrasion, periorbital contact dermatitis, periorbital pain, and periorbital edema. The non-ocular AEs were back pain, basal cell carcinoma, and headache (three participants). Refer to **Table 39** and **40**. All "run-in" phase ocular and periorbital AEs were reported as mild in severity except for one (nasal abrasion in Participant (b)(6)). Refer to **Table 41** and **42** for the severity levels and device relatedness designations for the "run-in" phase AEs.*

*Please note that the sponsor provided additional information related to periorbital pain in **Table 39** on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

7.5.2.4 Device Defects

In CP-X19, six of the 1113 (0.5%) goggles dispensed were reported as defective.

- Goggle defects (N=6)

  Four of these defects were attributed to "manufacturing errors" and two attributed to "component failures." The two component failures were described as the "strap stitching" becoming undone on one goggle and a "buckle snap" breaking during overnight wear. The four manufacturing errors were described as 1) three instances of insufficient sealant being applied to the lens/seal interface of the goggle, leading to a compromised seal or a dislodged lens; 2) one instance of the nose bridge connection to the right goggle lens becoming compromised during home use. None of the goggle defects resulted in AEs.

- Pump defects (N=12)

  Six of these defects were reported as component failures and six as manufacturing errors. The component failures were described as 1) two instances of pumps with faulty circuit board assembly components that generated an error message, preventing NP delivery; 2) two defective right-side pumps, preventing NP delivery; 3) two pumps with software issues that prevented cellular connectivity, which did not impact NP delivery (note: cellular connectivity is unavailable in the commercial version of the device). The six manufacturing errors were described as 1) three pumps with damaged secure digital (SD) cards (one of these prevented NP delivery to participant (b)(6)); 2) one pump's housing being inadequately secured; 3) one having intermittent power compromise to the left-side pump due to an improperly crimped connection, preventing NP delivery; 4) one with an incorrectly entered serial number, which did not impact NP delivery but "complicated the collection of device usage data." Two defective pumps were not assigned to any participant and one pump failed "out of the box" before the participant could take the device home for use.

  Per the sponsor, "These manufacturing errors were addressed by adaptations in component specifications and the assembly process to minimize the likelihood of future occurrence, additional quality inspection steps were implemented, and manufacturing personnel were retrained."

FDA Commentary: *Additional details regarding the impact of the 12 pump defects (5.3%) reported among the 226 pumps that were dispensed for home use during the trial, as summarized above, were provided by the sponsor in response to deficiency 2.e of the* ***AINN deficiency letter*** *dated November 8, 2023.*

7.5.4 Visual field (VF) and Optical Coherence Tomography (OCT) Data from CP-X19

- Visual field (VF) testing

  In CP-X19, participants were scheduled to undergo VF testing (using the Humphrey Field Analyzer, 24-2 SITA Standard testing strategy) in both eyes at baseline (Day -14; Visit 1), Week 26 (Visit 6), and Week 52 (Visit 8). VF tests performed within 60 days of Visit 1 were not repeated at Visit 1.

FDA Commentary: *Revision 6 version of the CP-X19 protocol was provided in DENXXXXX2. Appendix 4 of the protocol ("Examination procedures, tests, equipment and techniques") included brief methodologies for performing VF testing (page 195,* ***Attachment 8****). In deficiency 1.a.v of the* ***AINN deficiency letter*** *dated November 8, 2023 conveyed the concern that CP-X19 was not designed with pre-specified methodologies and measures to detect glaucoma worsening. Deficiency 1.c of the same letter also conveyed the concern that CP-X19 was inadequately designed to robustly detect glaucoma worsening.*

In response to deficiency 1.c, the sponsor stated that "Version 2" of the protocol, dated December 3, 2019, "required visual field…testing and OCT [imaging] of the optic nerve head and retinal nerve fiber layer at Baseline, Week 26, and Week 52." The sponsor referenced the same instructions in Appendix 4 of the protocol, explaining that those instructions had been implemented "prior to initial subject enrollment" under Revision 2 of the protocol (dated December 3, 2019). Under Revision 2 of the protocol, the VF testing portion of Appendix 4 stated:

> *"Visual Field (24-2 SITA Standard): A visual field test will be completed OU. Fixation losses, false positive errors, and false negative errors should be ≤ 33% to qualify as a reliable visual field. If the field does not qualify as reliable, the visual fields must be repeated. If fixation loss exceeds 33% with repeated fields despite patient instruction and repositioning, a field may be considered reliable if the technician observes gaze tracking throughout the visual field examination to confirm and document good fixation."*

FDA Commentary Cont'd: *The sponsor then stated that "additional specifications were added…to maximize visual field reliability" in Revision 6 of the protocol (dated November 10, 2021). These are shown in* ***bold****:*

> *"Visual Field (24-2 SITA Standard): A threshold visual field test will be completed OU.* ***The following device settings are recommended to maximize reliability:***
>
> - ***SITA Standard 24-2 Algorithm***
> - ***White, Size III Stimulus***
> - ***Foveal Threshold ON***
> - ***Vertex Monitoring OFF***
> - ***The appropriate trial lens as defined by the perimeter should be used.***
>
> *Fixation losses, false positive errors, and false negative errors should be ≤ 33% to qualify as a reliable visual field. If the field does not qualify as reliable, the visual fields must be repeated. If fixation loss exceeds 33% with repeated fields despite patient instruction and repositioning, a field may be considered reliable if the technician observes gaze tracking throughout the visual field examination to confirm and document good fixation."*

These additional stipulations were not added until almost 23 months after CP-X19 was initiated. Therefore, the extent to which VF testing varied without these additional stipulations in place (i.e., prior to Revision 6 implementation) remains unclear.

If either eye demonstrated a loss in mean deviation (MD) ≥ 2.5 dB from the Day -14 measurement at the Month 6 time point, a repeat VF was to be performed at Month 9. If this MD loss was observed at Week 52/Month 12, a repeat VF was to be performed at an unscheduled visit after trial exit even if outside the 60-day window.

FDA Commentary: *Please note that the requirement to report MD worsening ≥ 2.5 dB compared to Day -14 (as an AE) was not added to the protocol until Revision 6 (dated November 10, 2021). This was also noted as a concern in deficiency 1.c of the* ***AINN deficiency letter*** *dated November 8, 2023. This late modification to the protocol introduces uncertainty regarding how glaucoma worsening was assessed during the trial.*

In the DENXXXXX1 ***decline letter*** *dated September 10, 2021, FDA previously conveyed concerns regarding how glaucoma progression was assessed during CP-X10. In the QXXXXX4 FDA feedback (****letter*** *dated April 29, 2022; related to the September 10, 2021 DENXXXXX1 decline deficiencies and the sponsor's newly proposed clinical trial, Protocol CP-X24), FDA provided the sponsor with specific recommendations for assessments to determine possible glaucoma progression (e.g., OCT imaging, VF testing, clustering of VF assessments, addressing potential participant testing fatigue, etc.) for the sponsor's new proposed clinical trial (CP-X24). It should be noted that three of the four SGEs acknowledged the inherent noisiness of VF data and emphasized that this would need to be accounted for in the design of a new trial. In DENXXXXX2, the sponsor presented results of the CP-X19 trial (which had been ongoing at the time of FDA's QXXXXX4/SXX1 review) instead of those from the previously-proposed CP-X24 trial.*

Deficiency 1.c of the ***AINN deficiency letter*** *dated November 8, 2023 noted that VF testing was scheduled at only three points across the trial duration with no pre-specification of "clustering" of tests at a given time point (to account for inherent testing variability of VFs), a recommendation previously conveyed in the QXXXXX4 and QXXXXX4/S001 feedback.*

In response, the sponsor stated, "FDA's feedback to address VF noisiness was provided when CP-X19 was nearly complete…and related to a potential study [that] the Company was considering for the future."

The sponsor states that the trial was not designed to assess glaucomatous progression (page 17, DENXXXXX2/SXX1).

The summary of VF MD results reported in the CP-X19 trial at Baseline (Day -14), Week 26, and Week 52 is shown in **Table 44**.

Worsening in VF MD ≥ 2.5 dB was reported in seven participants at Week 26 (four study eyes and five control eyes) and in four participants at Week 52 (three study eyes and three control eyes).

- Optical coherence tomography (OCT) imaging

In CP-X19, participants were scheduled to undergo OCT imaging of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) in both eyes at baseline (Day -14; Visit 1), Week 26 (Visit 6), and Week 52 (Visit 8). OCT scans performed within 60 days of Visit 1 were not repeated at Visit 1. There was no specification in the CP-X19 protocol that sites utilize OCT systems of the same manufacturer and model. Appendix 4 ("Examination procedures, tests, equipment and techniques") of the the protocol (Revision 6) provided the following instructions on OCT scan acquisition:

> "**OCT of ONH and RNFL:** An assessment of the optic nerve and retinal nerve fiber layer will be completed OU. This exam will be performed with an OCT per manufacturer instructions, and the resulting quality score must be acceptable per the user manual. If the acceptability criteria are not met, repeat OCTs will need to be performed."

FDA Commentary: *This portion of Appendix 4 in the protocol did not appear to provide details on how OCT scans should have been acquired (e.g., with regard to specific scan patterns used). Beyond instructing that the "quality score" of the scan "must be acceptable per" the OCT manufacturer's User Manual, there did not appear to be any other detailed instructions to sites on verifying sufficient image quality.*

In Deficiency 1.a.iv of the ***AINN deficiency letter*** *dated November 8, 2023, it was noted that the study report for CP-X19 originally provided in DENXXXXX2 did not include specific discussion or summary presentation of OCT data; additional information was therefore requested.*

In response, the sponsor states, "No formal quantitative analysis of OCT data was performed as part of the CP-X19 analysis plan. The OCT images were included alongside the VF examinations for the post-hoc analysis performed by the VFRC. The VFRC's primary analysis included VF testing over time by independent, masked readers. The secondary analysis of the VF data included the adjunctive use of OCT imaging if it was of sufficient quality. Collectively, the VFRC used both VF and OCT to determine if there was evidence of disease progression at Week 52. As there was no standardization of OCT equipment used in the study, the only value available for all subjects from OCT testing is retinal nerve fiber layer (RNFL) thickness. Post-hoc assessment of changes in RNFL thickness for the study and control eyes of all 62 subjects who completed the Week 52 Visit showed no differences in either the study or control eyes… There was a single instance of OCT RNFL thinning ≥ 10 µm at Week 52 compared to baseline that occurred in a control eye. However, the OCT quality was poor (signal strength 4/10 at Week 52 versus 8/10 at Baseline)." Refer to ***Table 45*** *for the baseline and Week-52 mean RNFL thickness values in the study and control eyes.*

FDA Commentary Cont'd: *Note that it is unclear whether these RNFL thickness (RNFLT) values represent global RNFLT values or sectoral values. No instructions in the protocol were provided to investigators regarding how to interpret OCT scans acquired on the CP-X19 participants. Therefore, it is unclear whether investigators analyzed localized (i.e., not global) RNFLT values to determine how they may or may not correspond to known areas of glaucomatous optic nerve head rim tissue loss and/or glaucomatous patterns of visual field loss. In addition, no detailed information or case narrative was provided for the participant who was observed with ≥10 µm of RNFLT thinning at Week 52. While the sponsor states that the signal strength of the Week-52 scan was poor, the sponsor did not clarify whether the investigator repeated the scan (as instructed in the protocol) or collected other relevant clinically information to determine whether the RNFLT thinning was artifact or real.*

The Panel will be asked if long-term safety of the safety of the device has been demonstrated based on the availability of the one-year safety data.

7.5.3 IOP by Goldmann applanation tonometry (GAT) before/after in-office NP:

Table 43 shows IOP measured using GAT prior to and immediately following in-office NP application on Day -14, Day 0, Week 26, and Week 52. The difference between the mean pre-NP and post-NP IOP after NP application as compared to prior to NP was ≤ 1 mmHg in both the study and control eyes.

FDA Commentary: *The results of* ***Table 43*** *are similar to those shown in* ***Table 9*** *from the CP-X10 trial provided in DENXXXXX1.*

7.5.5 Visual field (VF) and Optical Coherence Tomography (OCT) Data CP-X19 – Post hoc analysis

In the CP-X19 study report originally provided in DENXXXXX2, the sponsor provided information from a *post-hoc* assessment of available Week-26 and -52 VF and OCT data. The sponsor stated that this was performed "to further characterize potential differences in glaucomatous progression in study vs. control eyes over the course of the [CP-X19] study." The assessment was performed by the University of Iowa Visual Field Reading Center (VFRC). The VFRC was requested to also perform the same post-hoc assessment on the VF data collected in the CP-X10 trial (see **Section 7.5.6**).

- Methodology (described in the VFRC report dated December 16, 2022)

"Three senior readers from the VFRC…participated in the analysis. Two readers analyzed each set of patient data. If the two readers did not agree, the third reader served as an adjudicator." The three readers were masked to the eye assigned to treatment with the OPAP device. The two readers made a determination as to whether the series of VFs had improved, stayed the same or worsened. Following this, a second analysis was done in the same manner as before, but with addition of the OCT data. Last, readers determined whether one eye progressed more than the other. When the two readers differed in their analysis outcome, an adjudicator read and provided the same analysis. If there was agreement of 2 of the 3 readers, the majority ruled. If the readers and adjudicator could not agree, the 3 readers met and adjudicated the readings together. The decision of the readers was in the form of "progression," "no progression," "indeterminable," or "not applicable if the necessary examination data was insufficient or unavailable."

The sponsor provided the data to the VFRC "in the form of printed, de-identified, masked visual field and OCT examinations." Then, the VFRC readers "'cleaned' the data from each eye of each subject, eliminating [VF] examinations and OCT images of insufficient quality, including fields with perimetric artifacts and other errors such as inappropriate lenses used or wrong test strategy done. Unreliable visual field examinations disqualified the eye from both analyses while an unanalyzable OCT disqualified the eye from the second analysis. OCT scans were also 'cleaned' and those with insufficient examinations with poor signal strength and artifacts were eliminated."

FDA Commentary: *Please note that the VFRC report in the original CP-X19 study report did not provide details on what criteria were specifically used to determine that a VF or OCT exam was "insufficient." Details on how the graders determined progression and maintained independence from each others' assessments were also not provided in the VFRC report. These missing details were also noted as a concern in Deficiency 1.a.v of the* ***AINN deficiency letter*** *dated November 8, 2023. Deficiency 1.a.v also conveyed the concern for bias introduced by the post-hoc nature of this analysis.*

In response, the sponsor acknowledged that the analysis was post-hoc in nature, but "bias was minimized because procedures for image analysis were established prior to initiation of VFRC's work, the data provided for VFRC review were masked to treatment assignment, and multiple readers reviewed images independently." The following new details to the methodology presented above (from the original CP-X19 study report/VFRC report) were provided:

- *To assess the VF series – "Since variability increases with visual field damage, the readers, all experienced in the range of perimetric variability, made judgements that were influenced by the amount of visual field damage. If the baseline Mean Deviation (MD) was better than -3.5 dB, 2 dB or more of worsening was considered to be significant, if the initial MD was between -3.5 and -10 dB, 3 dB or more worsening was required. If MD was worse than -10 dB, a 4 dB worsening was required (see reference). Reader judgement, with initial damage being considered, was used for defects that were worsening or improving in size or depth." The aforementioned reference is a publication titled "The Repeatability of Mean Defect with Size III and Size V Standard Automated Perimetry" (Wall M et al. Invest Ophthalmol Vis Sci 2013;54:1345-1351); note that the primary author is one of the three readers.*

- *To assess OCT scans – "[RNFLT] measures were called unchanged if the thickness varied less than 5 microns. The data were recorded in a spreadsheet organized by study subject and then by right eye and left eye." No reference or further rationale was provided in the response to support this 5-micrometer change. Please also note that the number of CP-X19 participants who were observed to have ≥5 µm of RNFLT thinning was not provided in the response.*

FDA Commentary Cont'd: *Deficiency 1.b of the November 8* ***AINN deficiency letter*** *noted that using only the VFs and OCT scans collected during the trial (i.e., over 52 weeks) to make the determination of glaucoma progression may not be sufficient to make a definitive determination of glaucoma. It is unclear if the VFRC readers were provided additional clinical information (e.g., results of direct examination of the optic nerve, review of prior diagnostic information over a longer stretch of time than 6-12 months) to supplement their assessments.*

In response, the sponsor states, "This multi-center study enrolled subjects with a diagnosis of normal tension glaucoma consistent with the American Academy of Ophthalmology (AAO)-preferred practice pattern guidelines. All study investigators were either fellowship-trained in glaucoma and/or regularly evaluate, diagnose, and manage patients with glaucoma. Optic nerve head evaluation was performed regularly through the study. If a subject had evidence of progression or risk factors suggestive of progression based on examination findings (e.g., disc hemorrhage, increased cup-disc ratio, or focal thinning) at the Week 26 or Week 52 Visit, this would have been identified and recorded in the study data. Given that glaucoma severity and disease staging is based on VF findings, the use of VF testing represents the functional standard for evaluation of disease progression. The use of adjunctive OCT imaging helps to evaluate for structural evidence of progression in patients with glaucoma and provides objective information to complement the subjective nature of VF testing. In clinical practice, glaucoma progression is typically determined by concomitant structural and functional loss. There is no widely accepted mean deviation threshold value for assessment of VF progression in patients with glaucoma."

The Panel will be asked given the methodology and post hoc nature of all VF and OCT analyses, do the available data demonstrate reasonable assurance of safety.

- VFRC analysis results

  68 of 93 participants (73.1%) had VF examinations at "glaucoma progression time points." 62 participants completed the Week-52 visit. Six participants completed the Week-26 visit, but exited prior to trial completion. A total of 418 VFs and 392 OCT examinations were analyzed (**Table 46**).

  The VFRC reported that "86.0% of eyes had perimetry results deemed of sufficient quality for analysis. Progression was observed evaluating VFs alone in 2 eyes of 1 subject (b)(6) . When analyzing OCT as a supplemental data to the VFs, progression was not observed." In the CP-X19 study report originally provided in DENXXXXX2, the sponsor reported that, of "the 62 subjects who completed the study, VF series sufficient for analysis of glaucomatous progression were present for 79.0% (n = 49) of study eyes and 72.6% (n = 45) of control eyes." Refer also to **Table 47**.

Seven (7.53%) participants at Week 26 (four study eyes and five control eyes) and four (4.3%) participants at Week 52 (three study eyes and three control eyes) were reported with worsening in VF MD ≥ 2.5 dB compared to baseline.

- The VF data from four of the seven (57.1%) Week-26 participants were determined by the VFRC to be "insufficient for analysis." In the remaining three of the seven, "no progression" was determined for either eye.

- The VF data from two of the four Week-52 participants (50.0%) were determined by the VFRC to be "insufficient for analysis." In the remaining two participants, VF data for the right eye of one (Participant (b)(6)) was "insufficient for analysis while the contralateral eye did not demonstrate any progression," while in Participant (b)(6), progression was not found in the right eye and "progression in the left eye was indeterminable."

This information is also summarized in **Table 48**. As seen in **Table 47**, the RC found two left eyes to be "indeterminable" for progression by OCT+VF.

FDA Commentary: *The VFRC could not definitively determine whether glaucoma had progressed in half of the participants who completed the CP-X19 trial and who were found to have ≥2.5 MD loss (compared to baseline), and in over half (57.1%) of those who completed at least half the trial (through Week 26) and who were found to have ≥2.5 MD loss. This is a source of uncertainty that was mentioned in Deficiency 1.d of the* ***AINN deficiency letter*** *dated November 8, 2023 (see additional discussion on Deficiency 1.d below). Deficiency 1.a.i of the November 8 letter requested information on which of these "indeterminable" eyes were study vs. control eyes.*

In response to Deficiency 1.a.i, the sponsor stated, "Evidence of progression was indeterminable in the control eye of [three] subjects." Please refer to ***Table 49****. However, it is unclear whether these three CP-X19 control eyes deemed "indeterminable" were part of the six participants who exited early or completed the trial. It was also noted that* ***Table 49*** *lists one left eye as "indeterminable" by VF examination alone and two left eyes as "indeterminable" by VF and OCT combined; this contradicts* ***Table 47*** *in which the number of left eyes deemed "indeterminable" by VF alone was listed as zero.*

Please note that the sponsor provided an updated ***Table 49*** *to address this contradiction on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

***FDA Commentary Cont'd**: Given that 62 of 93 randomized participants completed the 52-week trial (33% dropout rate), and that approximately 25% of VF examinations in this already-limited cohort were found to be "insufficient," it is unclear whether the trial is adequately sized and of sufficient duration to answer the question about glaucoma progression. Concern related to the limited sample size was communicated in Deficiency 1.d of the letter **AINN deficiency letter** dated November 8, 2023. In response to Deficiency 1.d, the sponsor stated,*

> *"Other than optic nerve examination via ophalmoscopy [sic], which showed no change in cup-to-disc ratio and no optic disk hemorrhages, the only data collected in the CP-X19 Study relating to the evaluation of glaucoma worsening or optic nerve damage is the VF and OCT imaging data that was summarized and presented in the Clinical Study Report. These data, in entirety, were analyzed by the VFRC, whose readers were masked to treatment assignment. **The CP-X19 Study was not designed to assess whether 52 weeks of nightly device wear has an impact on glaucomatous disease progression**; rather, it was designed to evaluate the safety and IOP-lowering effectiveness of NP application (via the OPAP) for adult patients with NTG during 52 weeks of use. The sample size calculation for this study was based on the primary effectiveness endpoint and then adjusted for the secondary effectiveness endpoint."*

*As discussed in FDA Commentaries in **Sections 7.5.4 and 7.5.5**, there are remaining concerns related to the use of this retrospective reading-center analysis which may not be robust enough to constitute a "ground truth" for determining glaucoma progression. Overall, the post-hoc nature of this analysis and potential for bias introduces uncertainty to answering the question regarding possible worsening of glaucoma associated with device use.*

The Panel will be asked given the methodology and post hoc nature of all VF and OCT analyses, is there sufficient evidence to demonstrate a reasonable assurance of safety of the use of the device. The Panel will also be asked if a reasonable assurance of long-term safety has been demonstrated based on the availability of the one-year safety data.

7.5.6 Visual field (VF) and Optical Coherence Tomography (OCT) Data – CP-X10 – Post-hoc analysis

The sponsor provided information from a *post-hoc* assessment of available VF and OCT data collected in the 90-day CP-X10 trial ("Apollo study," presented in DENXXXXX1) as part of the CP-X19 study report originally provided in DENXXXXX2. Please refer to **Section 7.5.5**: Methodology, for the discussion of the methodology used by the VFRC.

The analysis of the CP-X10 VF and OCT data provided by the VFRC is summarized in **Table 50**. A total of 372 VF examinations and 364 OCT scans from 58 participants were analyzed. The VFRC reported that 90.5% of eyes had perimetry results that were deemed of sufficient quality for analysis. Progression based on evaluating VFs alone was determined in two eyes of two participants; when OCT data was factored in as supplemental data to the VF examinations, no progression was reported. Four eyes of three participants were designated as "indeterminable" for progression: three based on VF examinations alone (two right eyes, one left eye) and three based on both VF examinations and OCT scans combined (one right eye, two left eyes). Two eyes were reported for which one "progressed more" than the other and three eyes were "indeterminable" for this particular determination.

FDA Commentary: *The sponsor did not identify whether the two CP-X10 eyes that "progressed more," the six eyes found "indeterminable," and the one right eye found to have progression were study eyes or control eyes. Deficiency 1.a.i of the* ***AINN letter*** *dated November 8, 2023, requested this clarification on the CP-X10 eyes deemed "indeterminable." In response, the sponsor stated that "cases in which the quality of the testing was sufficient, but [for which] the readers were unable to determine whether progression was present were categorized by the VFRC as 'indeterminable.'" The sponsor also provided a table (****Table 51****) showing the "indeterminable" status of the four eyes of three participants (mentioned above). However, this table contradicts the summary table for CP-X10 provided in the VFRC's original report (****Table 50****). In* ***Table 51****, both right and left eyes of CP-X10 Participant* (b)(6) *were "indeterminable" by both VF examination alone and by VF and OCT combined, the left eye of CP-X10 Participant* (b)(6) *was "indeterminable" by VF and OCT combined, and the left eye eye of CP-X10 Participant* (b)(6) *was "indeterminable" by VF examination alone. Hence,* ***Table 51*** *lists one right and two left eyes "indeterminable" by VF alone while* ***Table 50*** *shows two right and one left eyes.*

Please note that on February 15th, 2024, the sponsor revised ***Table 51*** *to address this inconsistency. However, this version of Table 48 was not provided in DENXXXXX2/SXX1 and has not been reviewed by the FDA.*

In CP-X10, 58 of 64 participants were available for analysis at the final visit (Day 90). Of these 58, six (9.4%) were reported with ≥-2.5 dB MD loss from baseline. Three of these six (50.0%) had VF examinations that were deemed "insufficient for analysis" by the VFRC. In the other three, two were not reported to have progression in either eye, and in one, the right eye was determined to have progression but not in the left eye. Note that for four of six (66.7%) participants who were reported with ≥-2.5 dB MD loss from baseline to Day 90, the VFRC analyzed "all available VF [and] OCT" information for this subset, including "pre- and post-study VFs…if available."

***FDA Commentary Cont'd**: Deficiency 1.a.ii of the **AINN deficiency letter** November 8, 2023, requested clarification on the CP-X10 participants in whom the VFRC reported one had progressed more than the other. In response, the sponsor stated that the VFRC identified two participants at the Day 90 time point with evidence of VF progression in one eye relative to the other eye (CP-X10 Participants (b)(6) study eye and (b)(6) control eye); in each of these participants, "the progression displayed via VF testing could not be confirmed when evaluating adjunctive OCT testing."*

*Deficiency 1.a.iii of the **AINN deficiency letter** dated November 8, 2023, requested additional information on how many additional VF and OCT tests on those with ≥2.5 MD loss outside of the CP-X10 trial window were assessed by the VFRC. In response, the sponsor explained that "additional visual field and OCT testing" was assessed by the VFRC for four participants. This is summarized in **Table 52**. Only one participant had pre- and post-trial data provided to the VFRC. For two participants, no pre-trial data was provided, and for one, no post-trial data was provided.*

There is remaining concern that analyzing all available pre-trial and post-trial VF and OCT information on only those with ≥-2.5 dB MD loss, instead of all participants, may lead to under-reporting of glaucomatous progression in the presence of lesser MD loss. In addition, a cutoff of 2.5 dB loss on MD may not be the only necessary criterion to trigger greater scrutiny of the participant for glaucoma progression.

*The same limitations of the post-hoc analysis identified for CP-X19 largely apply to this CP-X10 analysis. As mentioned in sub-part (a)(i) of the DENXXXXX1/S002 **decline letter**, the CP-X10 "trial was not designed to collect the additional necessary VF testing…to distinguish between true glaucomatous versus artifactual change"; in Deficiency 1 of the DENXXXXX1/SXX1 **AINN letter**, FDA stated, "the trial was inadequately designed to distinguish between VF change that is due only to 'noise' versus clinically real change…the absence of a correlative C/D increase does not rule out real VF change." This "inadequacy" refers to the lack of repeated VF testing throughout the 90 day-trial and the lack of pre-specified instructions to CP-X10 investigators regarding assessment for glaucoma progression all throughout the trial (similar to some concerns noted for Protocol CP-X19). There are also the additional limitations that 1) it is difficult to detect glaucoma progression in such a short period of time as 90 days, and 2) it is likely that CP-X10 was undersized to be able to do so.*

7.6 Effectiveness Results

7.6.1 Primary and Secondary Effectiveness Endpoints

The primary effectiveness endpoint is the proportion of eyes with IOP reduction of 20% or greater at 52 weeks (Visit 8) as measured via pneumotonometry with Excursion goggles worn from "before" to "during" application of negative pressure during in-clinic visit.

The pre-specified hypothesis for the primary effectiveness endpoint is the proportion of eyes with IOP reduction of 20% or greater at 52 week (Visit 8) in-clinic visit is higher in the treatment group compared to the control group at a one-sided alpha level of 0.025. The corresponding statistical hypotheses are as follows:

Null Hypothesis: $\pi T_1 - \pi F_1 \leq 0$
Alternate Hypothesis: $\pi T_1 - \pi F_1 > 0$

The πT_1 and πF_1 are the proportion of eyes at the Week 52 in-clinic visit with IOP reduction ≥ 20% compared to baseline for the treated and control eyes, respectively.

The pre-specified primary analysis population for the primary effectiveness endpoint is the mITT population defined as all randomized patients who have at least one full application of NP. Among the 93 patients in the mITT population, 33 of them are with missing primary effectiveness endpoint measurements, resulting in a 35.5% missing rate for the two study groups. With all missing values imputed as "non-responders" per the pre-specification, 58.1% (54/93) of treated eyes have ≥ 20% reduction in IOP during NP application, as compared to 1.1% (1/93) of control eyes, which is statistically significant ($p < 0.001$). Please refer to **Figure 14**. The difference between groups achieving ≥20% reduction in IOP during NP application is 57.0%, with a 95% confidence interval (CI) of 45.4% to 66.2%" (p. 65, Vol. VII).

FDA Commentary: *In the worst-case scenario where the missing control eyes are imputed as responders and the missing treated eyes are imputed as non-responders, the primary effectiveness endpoint is still met.*

FDA Commentary: *The results of* ***Table 53*** *indicate that the proportion of those achieving 20% lowering is lower than the values reported in CP-X10 (from DENXXXXX1), which was also a shorter trial duration (90 days):*

- *In the trial of CP-X10, 81.3% (52/64) of the treated eyes in the mITT population achieved this primary effectiveness endpoint.*
- *In this CP-X19 trial, 63.4% (59/93) of the treated eyes in the mITT population achieved the primary effectiveness endpoint.*

Secondary effectiveness endpoints: The secondary effectiveness endpoint is the proportion of eyes in the mITT population with Week-52 sleep lab IOP (measured supine during NP application, via excursion tonometry, at 11:00 pm, 2:00 am, and 5:00 am, all within ± 60 minutes of the specified time point) reduction of 20% or greater compared to baseline IOP (measured prior to NP application).

The secondary endpoint is tested after the primary effectiveness endpoint achieves statistical significance. The pre-specified hypothesis for the secondary effectiveness endpoint is the proportion of eyes with IOP reduction of 20% or greater at 52 week (Visit 8) in sleep lab is higher in the treatment group compared to the control group at a one-sided alpha level of 0.025. The corresponding statistical hypotheses are as follows:

Null Hypothesis: $\pi T_2 - \pi F_2 \leq 0$
Alternate Hypothesis: $\pi T_2 - \pi F_2 > 0$

The πT_2 and πF_2 are the proportion of eyes at the Week 52 in sleep lab visit with IOP reduction ≥ 20% compared to baseline for the treated (study) and control eyes, respectively.

The pre-specified primary analysis population for the secondary effectiveness endpoint is the mITT population. With all missing values imputed as "non-responders," 63.4% (59/93) of study eyes achieved ≥ 20% reduction in IOP compared to 3.2% (3/93) of control eyes, which is statistically significant ($p<0.001$). The difference between groups achieving ≥ 20% reduction in IOP during NP application is 60.2%, with a 95% CI of 48.6% to 69.3% (p. 66, Vol. VII). This

FDA Commentary: *It was noted that the performance of the primary effectiveness endpoint in the CP-X19 pivotal study (i.e., CP-X19 58.1%=45/93 in the treated eyes vs 1.1%=1/93 in the control eyes) was different than that in the prior supplemental study (i.e., CP-X13: 46.7%=7/15 in the treated eyes vs 33.3%=5/15 in the control eyes). In deficiency 6 of the* ***AINN deficiency letter*** *dated November 8, 2023, the sponsor was asked to clarify these results. In response, the sponsor provided a summarized comparison of the two study designs and outcomes in DENXXXXX2/SXX1. The sponsor noted two factors contributing most to the performance differences in terms of the proportions of eyes with IOP reduction ≥ 20% during NP application:*

- *The limited number of eyes in the CP-X13 study (N=15)*
- *Differences in goggle design. The smaller goggles evaluated in CP-X13 resulted in suboptimal fit, which affected both intra-goggle NP application and excursion tonometry methodology*

The sponsor used Fisher's exact test to evaluate the difference in outcomes among the study sites for the CP-X19 study. The results indicate a statistically significant difference (p > 0.15) among sites in the proportion of study eyes achieving in-clinic IOP reduction ≥ 20% during NP application at Week 52, which means there is likely a site effect for the primary effectiveness endpoint. This concern was communicated as deficiency 7 in the ***AINN deficiency letter*** *dated November 8, 2023. In response, the sponsor noted in DENXXXXX2/SXX1 that the overall proportion of study eyes achieving in-clinic IOP reduction ≥ 20% during NP application in-clinic was 58.1% in the mITT population. The sponsor conducted a revised site poolability test only on sites with at least 5 subjects (number of sites =8) and no site effect was identified (p-value=0.489).*

information can be found in **Table 54** and **Figure 15**. Descriptive statistics of pre- and post-NP excursion tonometry IOPs for initial and final sleep lab visits are provided in **Table 55**.

FDA Commentary: *The proposed IFU states the device lowers intraocular pressure (IOP). The data from the Protocol CP-X19 clinical trial showed that there was no clinically meaningful change from baseline to post-device use across all time points in both the in-office and sleep lab study visits using Goldmann applanation tonometry (GAT). Furthermore, the change in the study eyes was similar to that in the control eyes. Participants were allowed to remain on their usual IOP-lowering medication regimen and previous IOP-lowering procedures such as laser trabeculoplasty or non-bleb-forming surgeries were allowed. Although the fellow eye of the participant was used as the control eye, there were no measures in CP-X19 to ensure that the fellow eye's baseline clinical status (e.g., with regard to glaucoma status, the number and nature of IOP-lowering treatments for each eye) will be required to be similar to that of the study eye.*

This conventional IOP measurement is defined by the pressure difference between the inside of the anterior segment of the eye and the environment immediately outside of the eye—by convention (i.e., under typical circumstances), atmospheric pressure—as measured by applanating the cornea. However, when using the MPD, the environment immediately outside of the eye is a negative pressure (NP) environment, i.e., below atmospheric pressure. Hence, in this trial, conventional IOP is the "transcorneal pressure difference" (TCPD) relative to the within-goggle NP environment.

*An alternative IOP parameter was devised by the sponsor to measure IOP while the device is in use (i.e., with negative pressure [NP] on), as the Goldmann applanator cannot be used while a patient is wearing the goggles. This parameter was found to be lowered only while the device is in use and rebounded once the device was turned off. It is based on this alternative IOP and measurement of it during use that the sponsor states the primary effectiveness endpoint was met. However, the sponsor defines this alternative parameter as TCPD relative to atmospheric pressure without accounting for the NP microenvironment. Although the data demonstrated that this alternative IOP is lowered temporarily when the device is in use, the sponsor previously acknowledged (DENXXXXX1/S002) that conventional IOP actually increases by approximately 21.7% - 26.9% with device use. For the CP-X19 study, the sponsor reports (DENXXXXX2/SXX1) this increase is approximately 23.6% to 33.0% (**Table 56**). Hence, IOP defined in one way increases, while IOP defined in another way decreases. Whether this alternative IOP as measured using the sponsor's approach can appropriately serve as a surrogate endpoint is unclear. The clinical trial was not designed to demonstrate slowing or halting of glaucoma progression, so it remains unknown whether there is benefit to raising the conventional IOP and lowering this alternative IOP. It is also unclear whether the latter, when achieved only temporarily, has benefit.*

The Panel will be asked to discuss whether there is clinical benefit to lowering of this alternative IOP while also increasing TCPD.

8. Report of Prior Investigations

The sponsor provided the following list of prior investigations in support of their De Novo:

- CP-XXX: Pilot Proof of Concept Study (GEN0 Device)
- CP-XX1: Short-Term Exposure Study (GEN0 Device)
- CP-XX4: Secondary Proof of Concept Study in Patients Implanted with a Telemetric, IOP-Measuring Device (GEN1 Device)
- CP-XX5: Short-term Wear at 3 Atmospheric Pressure Reduction Levels Study (GEN1 Device)
- CP-XX6: Longer-Term Wear Safety Study at -10 mmHg Atmospheric Pressure Reduction (GEN1 Device)
- CP-XX7: Overnight Safety Study (7-Days of Nightly -10 mmHg Negative Pressure Application (GEN1 Device)
- Pneumatonometry and Tonometer Tip Cover Study
- Pneumatonometry with Negative Pressure Application
- Closed Eyelid Tissue Transfer Study
- Living Eye Project Pressure Study (GEN2B Device)
- CP-X13: Evaluation of the Safety and Effectiveness of Negative Pressure Applied Nightly by BGS to Lower IOP (GEN2A Device)
- Short-Term Pattern ERG Changes with Negative Pressure Application (GEN1 Device)
- Cadaver Retrobulbar Pressure Study (GEN2B Device)
- Laser Speckle Flowgraphy Blood Flow Study (GEN2B Device)
- OCT-A Blood Flow Study (GEN2B Device)
- Metabolic Changes Using Flavoprotein Fluorescence Study (GEN2B Device)
- CP-X18: Short-Term Nocturnal IOP Study (GEN2B Device)
- CP-X10: EXPLORER Study13 (GEN2B Device)
- CP-X22: Ranger Study (GEN2B Device)
- CP-X23: Endure Study (GEN2B Device)
- CP-X24: CONFIRM Study

While many of these studies had previously been submitted and reviewed by the FDA in prior submissions, the following studies were reviewed as part of the current De Novo:

- CP-XX4, Secondary Proof of Concept Study in Patients Implanted with a Telemetric, IOP-Measuring Device (GEN1 Device)
- Short-Term Pattern ERG Changes with Negative Pressure Application (GEN1 Device)
- OCT-A Blood Flow Study (GEN2B Device)
- Metabolic Changes Using Flavoprotein Fluorescence Study (GEN2B Device)
- CP-X18: Short-Term Nocturnal IOP Study (GEN2B Device)

- CP-X22: Ranger Study (GEN2B Device)
- CP-X23: Endure Study (GEN2B Device)
- CP-X24: CONFIRM Study

FDA Commentary: *Additional clarifications regarding the above studies were provided by the sponsor in an email dated October 10, 2023. The summaries below are based on the updated information.*

Note that CP-X24 was provided in DENXXXXX2/SXX1 in response to deficiency 4.a.i of the ***AINN letter*** *dated November 8, 2023.*

Metabolic Changes Using Flavoprotein Fluorescence Study (GEN2B Device)

The sponsor provided the following article: Sun et al. (2022) Structural and Metabolic Imaging After Short-term Use of the Balance Goggles System (BGS) in Glaucoma Patients: A Pilot Study. *J Glaucoma* 31:634–638. The sponsor intended to show that short-term use (1 month) of the BGS device does not cause observable anatomical changes in OCT imaging and may improve the metabolic status of the retina based on flavoprotein fluorescence (FPF) measured by a fundus imaging device, OcuMet Beacon.

Study Overview: The reported study was a single-center, open-label, single-arm and nonrandomized trial in which 8 eyes from 8 patients with open angle glaucoma (ranging from mild to severe) received a baseline evaluation including retinal imaging including OCT and OcuMet Beacon, then 1 hour of negative pressure application through the Balance Goggles System (BGS), followed by another retinal imaging with the same imaging modalities. Participants then used the BGS at home for 1 month and underwent another evaluation at the conclusion of the study using the same imaging devices used for the baseline evaluation. For the "metabolic" evaluation, the authors compared baseline FPF scores at the optic disc with those after 1-month BGS treatment.

Author's Conclusion: "There were no significant changes observable using conventional OCT imaging after short-term use of the BGS, although metabolic imaging using FPF may be a useful potential biomarker to complement existing investigations. Additional studies are warranted to further investigate these changes."

FDA Commentary: *The device used for evaluating the retinal metabolic status in the study is OcuSciences' OcuMet Beacon imaging device. The device was used to measure flavoprotein fluorescence (FPF) from fundus autofluorescent images. However, it should be noted that the OcuMet Beacon device has not been cleared by FDA. There are no imaging devices currently cleared for use in the U.S. for imaging of the mitochondrial flavoprotein signature (i.e., FPF) in the human retina. The sponsor has not provided evidence that the OcuMet Beacon device used in the study is able to measure FPF. Therefore, from FDA's perspective, the study provided by the sponsor does not provide sufficient evidence regarding the metabolic state of the retina after NP application, given that neither the diagnostic device used nor the novel biomarker evaluated have been validated. We conveyed our view on OcuMet Beacon in deficiency 5 of the* ***AINN deficiency letter*** *dated November 8, 2023. In response, the sponsor acknowledged that OcuMet Beacon has not been cleared by FDA. They state that the purpose of the study was to provide supplementary physiological evidence that the OPAP device lowers IOP when NP is applied by demonstrating an improvement in metabolic function using flavoprotein fluorescence. However, FDA's perspective is the interpretation of the results of study are still limited as FDA is not aware of any published data demonstrating that OcuMet Beacon is able to distinguish FPF from other sources of autofluorescence including the predominant one, lipofuscin, in the human retina.*

Short-Term Pattern ERG Changes with Negative Pressure Application (GEN1 Device)

Kudrna JJ, Ferguson TJ, Swan RJ, et al. Short-Term Steady-State Pattern Electroretinography Changes Using a Multi-Pressure Dial in Ocular Hypertensive, Glaucoma Suspect, and Mild Open-Angle Glaucoma Patients: A Randomized, Controlled, Prospective, Pilot Study. Ophthalmology and Therapy. Published online 2020:1-12.

Study Overview: This study evaluates the effects of the multi-pressure dial on steady-state pattern electroretinography (ss-pERG) parameters. The study is a randomized, controlled prospective, pilot trial in a private practice setting with ocular hypertensive (OHT), glaucoma suspect, and open-angle glaucoma (OAG) subjects.

Author's Conclusion: Following 2 h of MPD wear, the measured in MagnitudeD (MagD) and MagD/Mag ratio improved compared to control, suggesting that negative periocular pressure application to the anterior globe can lead to short-term improvement in one measure of retinal ganglion cell function.

FDA Commentary: *FDA identified several limitations of this study design. There is a concern that 9 subjects were included in the study, including 3 different diagnoses (OHT glaucoma suspect, and mild OAG), but no subjects with normal, healthy eyes were included in the study. No information is provided about the diagnostic criteria used to categorize the subjects, and no information is provided about the individual subjects' IOP levels, visual field loss, or IOP-lowering therapy. The inclusion of subjects with previous refractive surgery can potentially confound the results because their corneas are thinner and weaker than normal, and therefore are potentially subject to greater strain in response to the negative pressure. The failure to include normal subjects also limits the interpretability of the results as it is unclear whether any observed PERG effects are specific to glaucoma or elevated IOP.*

The authors of this article used a Diopsys ss-pERG (Diopsys, Pine Brook, NJ, USA) High Contrast Sensitivity protocol. There were numerous concerns identified regarding this protocol (i.e., description of stimulus conditions is incomplete, no information is provided about the viewing distance, spatial frequency, or orientation of the grating, or the visual angle subtended, the test procedure has no safeguards against bias, such as blinding the examiner to eye condition, or randomizing testing order, it was left up to the examiner's discretion to delete any responses not considered strong enough, with no criteria described for deletion.)

Overall, the effects of 1-3 hours of negative pressure on the pattern ERG response are nominal and the differences between the test and fellow eyes are likely statistically significant but it is unclear whether this is because the fellow eyes showed equally small effects in the opposite direction. It is unclear if the results would have been similar for normal subjects, since such subjects were not included in this study. Due to these limitations, there is uncertainty as to whether the study demonstrates that negative pressure significantly improves ganglion cell function, or that any such improvement is specific to glaucoma or elevated IOP. Also, it is not clear why lowering the IOP by a few mmHg should be expected to improve ganglion cell function in a cohort with a mean IOP of 17 mmHg, or why ganglion cell function should be reduced in the fellow eye that was not exposed to negative pressure.

OCT-A Blood Flow Study (GEN2B Device)

Multi-Pressure Dial Goggle Effects on Circumpapillary Structure and Microvasculature in Glaucoma Patients, Kamalipour A, Moghimi S, Inpirom VR, Mahmoudinezhad G, Weinreb RN. Ophthalmology Glaucoma. 2022 Nov 1;5(6):572-80.

Study Overview: The purpose of the study was to evaluate the effects of Multi-Pressure Dial (MPD) induced pressure changes on circumpapillary retinal nerve fiber layer (RNFL) and capillary density (CD) measurements in glaucoma patients using Optical Coherence Tomography Angiography (OCTA). The subjects for the study consisted of twenty-four patients with primary open angle glaucoma.

Spectral-domain OCT and OCTA imaging of the macula were performed the AngioVue imaging system (Optovue, Inc., Fremont, CA, USA, Version 2018,1,1,63). With this platform, Spectral-domain OCT and OCTA images are obtained from the same volumetric scans. This allows precise automated registration of OCT and OCTA images and provides quantified metrics for the analysis of the layer of interest.

Author's Conclusion: Circumpapillary CD measurements showed a dose-dependent increase with the induction of negative pressure while RNFL thickness measurements remained unchanged.

FDA Commentary: *The results show slight acute increases (up to a maximum of about 5% for -20 mmHg) in capillary blood flow after 2 minutes of negative pressure. This increase disappears immediately upon release of the negative pressure. No data are provided for blood flow changes after several hours of negative pressure, as would be consistent with the proposed clinical use of the device. Autoregulation mechanisms normally compensate for changes in IOP to maintain a consistent rate of blood flow. It is unclear whether the observed increases would have been sustained for longer negative pressure applications. Additionally, it is unclear whether the slight observed increases had any significant positive or negative effects on retinal function.*

The shortcomings of both the Short-Term Pattern ERG Changes with Negative Pressure Application (GEN1 Device) and OCT-A Blood Flow Study (GEN2B Device)studies are that they test only acute effects that are not comparable to the intended use of the device, the reported effects of the negative pressure are barely measurable and of unclear clinical significance, and the tested variables are not clearly related to the assessment of glaucoma progression.

Protocol CP-XX4- "Secondary Proof of Concept Study in Patients Implanted with a Telemetric, IOP Measuring Device (GEN1 Device)":

Study Overview: This was a prospective, single-site (Germany), 1-week trial to investigate the GEN1 version of the device in five participants "previously implanted with a wireless IOP-monitoring sensor (EYEMATE®, Implandata, Hannover, Germany). The wireless IOP sensor permits instantaneous and on-demand measurement of IOP" (p. 4/5, Attachment 1 of **Attachment 11**). Eligible participants underwent baseline IOP measurements via pneumotonometry and EYEMATE Telemetry and other baseline assessments (BCDVA, SLE, OCT, VF, Manifest Refraction, Subjective Assessment) on Visit 1 (Day -7). On Visit 2 (Day 0), participants wore the device for 8 continuous hours (with NP applied to one study eye and no NP to the fellow eye), and IOPs were checked intermittently throughout this period (hours 1, 4, and 7; four measurements per time point spaced 15 minutes apart) with the EYEMATE® (and excursion goggle-pneumotonometry at the beginning of the 8 hours, before and after 5 minutes

of NP). The final visit at Days 5 to 8 was conducted to evaluate for safety events. The NP level was programmed to target 50% of the baseline IOP value.

Author's Conclusion: The mean baseline IOPs were 22.8±4.3 mm Hg and 21.5±2.9 mm Hg by Eyemate and pneumotonometry, respectively. No descriptive information was provided on the specific NP levels used or on the wear time of each participant. During device use/NP on, the mean Eyemate IOP at the end of 8 hours was 16.7±4.1 mm Hg. 11 AEs were reported for all five participants. "The adverse events were primarily related to the device and included mild headache, lid edema/erythema, non-specific eye pain, itching, skin changes and conjunctival chemosis. One notable adverse event, which was evidence of herpes keratitis, was identified on screening and the patient did not proceed with the study. This was an unexpected adverse event and not felt to be related to the study. All adverse events were classified as mild and all events related to the device resolved without sequelae. No subjects that passed screening were unable to complete the entire duration of the study and all subjects completed every portion of the study protocol" (p. 23, Attachment 1 of **Attachment 11**). Of note, one participant "was removed from analysis after the study was completed because the data collected was deemed unsatisfactory by the investigators in the study. In this particular case (subject 6), the IOP values obtained via the wireless implanted IOP sensor had considerable variation from the IOP measurements obtained via pneumotonometry; these inconsistencies in measurement were present both on the screening

FDA Commentary: *The applicability of this data is unclear given that it was collected using a significantly different version of the device and that the device was used for only one day. The limited results (regarding IOP decrease while the NP is on, periorbital/adnexal AEs) presented here seem to be roughly consistent with that reported in CP-X10 and CP-X19.*

There was no discussion on the case of "raised IOP" (Participant (b)(6) *) reported in CP-XX4. Deficiency 5.a of the* ***AINN deficiency letter*** *dated November 8, 2023, requested clarification on why this report was designated as an "expected" AE and on whether the one participant with "raised IOP" is the same participant excluded post hoc from analyses. In response, the sponsor stated,* (b)(6) *was a 60-year-old female with a history of glaucoma who was using 3 topical IOP-lowering medications. At the baseline visit, her IOP via tonometry was 16.5 mmHg in the control eye and 19.0 mmHg in the study eye. The subject underwent 8 hours of NP exposure in the study eye at the second study visit. When she returned for the 1-week follow-up visit after her day of NP exposure, baseline IOP via pneumotonometry was elevated by 7 mmHg to 26 mmHg in the study eye and > 10 mmHg in the control eye. As IOP was elevated in both eyes (NP was applied to only 1 eye), and the study investigator advised the subject to resume topical glaucoma medications, then noted the AE resolved without sequelae, it is postulated that the subject had not used her ocular hypotensive medications prior to reporting to the 1-week visit."*

Note that this response does not address whether the data from Participant (b)(6) *was excluded post-hoc from the analyses.*

day and on the study day prior to initiation of negative pressure application" (p. 17, Attachment 1, of **Attachment 11**).

Protocol CP-X18- "Short-Term Nocturnal IOP Study (GEN2B Device)"
Goldberg JL, Jiminez-Roman J, Hernandez-Oteyza A, Quiroz-Mercado H. Short-term evaluation of negative pressure applied by the multi-pressure dial system to lower nocturnal IOP: a prospective, controlled, intra-subject study. Ophthalmology and Therapy. 2021 Jun;10:349-58

Study Overview: This was a prospective, single-site trial conducted in Mexico. 11 adult participants with open-angle glaucoma on a current regimen of a topical prostaglandin analog were recruited. The sponsor used the device in a sleep lab setting, and supine nocturnal IOPs by excursion pneumotonometry were measured at three time points over an 8-hour period. The NP level was based on 60% of the supine IOP value obtained prior to NP application. One eye was the study eye and the fellow eye was the control eye (no NP applied).

Author's Conclusion: The mean % IOP reduction was 35%. The authors state that "There were two adverse events that occurred during the study period. One subject had diarrhea during the study period which was self-limited and resolved without sequelae. Another subject had eye pain during the study period, and an examination revealed anterior uveitis for which the subject was treated with appropriate topical therapy." The authors state in the discussion section that the results show that the device "can still achieve meaningful IOP reduction in eyes currently receiving medical treatment." The case of anterior uveitis was not addressed. Among the control eyes, mean IOP was also lowered 2.3 mmHg, from 21.8±2.5 mmHg to 19.5±2.4 mmHg.

FDA Commentary: *The design of this trial is similar to that of CP-X19 (primarily with respect to obtaining IOP endpoints nocturnally in a sleep lab environment) except the trial mainly involved a single sleep-lab visit. Possible limitations of this study include the overall wear time during the 8-hour period and the single-visit design.*

Additionally, the report of anterior uveitis is notable, as conveyed in Deficiency 5.b of the ***AINN letter*** *dated November 8, 2023. In CP-X19, the sponsor states that "there were no reports of anterior [chamber] cells or flare, changes in iris appearance, or anterior chamber angle." As noted above, however, there were reports during CP-X19 of eye pain. In response to Deficiency 5.b, the sponsor stated that eye pain was reported by three participants* (b)(6) (b)(6) *study eye only,* (b)(6) *both eyes,* (b)(6) *study eye only). "In each case, the onset of eye pain appeared to be related to an increase in the OPAP NP setting and resolution of the complaint was achieved with a downward adjustment of the setting." This response suggests that the eye pain reports in CP-X19 were not believed to be due to intraocular inflammation, and no signs of intraocular inflammation were noted per the case narratives for* (b)(6) (b)(6) *and* (b)(6)

Protocol CP-X22- "Ranger Study"- "Negative pressure applied by the [MPD] to lower and modulate [IOP] in subjects with severe open angle glaucoma":

Study Overview: The goal of this study was to evaluate the safety and IOP-lowering effectiveness of negative pressure application for lowering and titrating intraocular pressure (IOP) in 61 severe open-angle glaucoma (OAG) patients. This was another prospective, single-visit trial, this time on participants with "severe" OAG. Eligible participants underwent two one-hour ("±15 minutes") treatment periods (in the study eye, while the fellow eye served as control/no NP applied). During the first hour, the programmed NP was 50% of the baseline IOP; during the second hour, 75%. GAT and pneumotonometry through the excursion goggles were performed similarly to how they were done in CP-X19 and CP-X10. The primary effectiveness endpoint was the proportion of participants who achieved ≥20% "IOP reduction (measured via pneumotonometry) during the application of [50%-of-baseline programmed] negative pressure compared to the IOP with Excursion Goggles on but prior to negative pressure application."

Sponsor's Conclusion: This trial "demonstrated that the MPD safely and effectively lowered IOP in eyes with severe OAG" (p. 203/236, Vol. VII).

FDA Commentary: *Similar to the other supporting studies provided, the utility of this data is extremely limited since it is based only on a one-time use of two hours of NP, albeit at a higher programmed setting. No durable conclusions can be made on effectiveness or safety with a single session of two hours of device use.*

The protocol described two "patient questionnaires" to be administered to participants. However, the protocol provided did not describe the specific items in either questionnaire. The results section of the study report also does not mention any results from the questionnaire administration. Additional information on these questions was requested in Deficiency 5.c of the ***AINN deficiency letter*** *dated November 8, 2023.*

In response, the sponsor stated that participants were asked the following two questions:

1) *At 50% NP application: Treatment with the MPD at the 50% negative pressure level lowered your IOP to ___. On a scale of 1-10 (with 1 being 'not at all' and 10 being 'absolutely'), how likely are you to wear this on a nightly basis at this level to achieve additional lowering of your eye pressure?*

2) *At 75% NP application: Treatment with the MPD at the 75% negative pressure level lowered your IOP to ___. On a scale of 1-10 (with 1 being 'not at all' and 10 being 'absolutely'), how likely are you to wear this on a nightly basis at this level to achieve additional lowering of your eye pressure?*

FDA Commentary Cont'd: *The sponsor stated, "At 50% NP application, the mean response value was 7.9 ± 2.3 (1 = not at all, 10 = absolutely), and 44/61 subjects selected a value of 8 or greater on the scale of 1-10. At 75% NP application, the mean response was very similar at 7.8 ± 2.5, with 42/61 subjects selecting a value of 8 or greater on the scale of 1-10. These questionnaires aimed to evaluate how patients felt about use of the OPAP as a treatment device for glaucoma." The significance of these responses is unclear. For example, it is unclear whether responses based on a single-session device-use experience can be generalized to those based on long- term experience.*

Protocol CP-X23- "Endure Study"- "Application of Negative Pressure by the Equinox Multi-Pressure Dial to Provide a Sustained Reduction in Intraocular Pressure (IOP) in Adult Subjects with Open-Angle Glaucoma":

Study Overview: The Endure study was a single-site prospective, controlled, randomized, evaluator-masked study to evaluate the sustainability of IOP reduction with continuous NP application via the OPAP over an extended duration (8 hours) in 10 subjects with OAG and IOP ≤ 21 mmHg. As with clinical studies CP-X19 and CP-X10, subjects were randomized such that one eye received treatment and the contralateral eye acted as a control (no NP treatment). After screening, subjects received an 8-hour period of continuous, uninterrupted [60%-of-baseline] NP application while wearing the Excursion version of the OPAP, which allowed for IOP measurement during NP application. Excursion tonometry was performed at 2-hour intervals and an additional IOP measurement was obtained immediately following cessation of NP at the conclusion of the 8-hour study period. Participants had open-angle glaucoma, including "normal tension glaucoma," with screening GAT IOP between 15 to 22 mm Hg with or without IOP-lowering medications. The effectiveness outcome of interest was "IOP reduction during sustained negative pressure application (as measured via pneumotonometry with Excursion goggles worn) at the time points of data collected every 2 hours of Visit 2." 10 participants were enrolled and nine completed the trial. The mean IOP measurements at various timepoints in the study and control eye can be found in **Table 57** and **Figure 16**.

Sponsor's Conclusion: This trial "demonstrated that the IOP reduction conferred by the OPAP is sustained throughout the device wear/NP application period. The IOP reduction exceeded 25% at each timepoint measured across 8 hours of continuous wear".

FDA Commentary: *Safety outcomes of interest are similar to those described for Protocol CP-X22 described above. The pre-NP and post-NP IOPs in both study and control eyes were slightly higher than baseline, as seen in* ***Figure 16****. There was lowering of the pneumotonometry IOP while NP was on. The limitations of this trial include the single-visit design and the small sample size.*

The Panel will be asked to discuss whether the observed IOP lowering during use supports demonstration of reasonable assurance of effectiveness as per the proposed indications for use.

Protocol CP-X24: Direct Manometric Measurement of Intraocular Pressure (IOP) During Application of Negative Pressure in Adult Subjects Undergoing Cataract Surgery

Study Overview: This was a prospective, single-arm, single-site basic physiological research study to evaluate the change in IOP as measured using manometry during periocular negative pressure (NP) application using the FSYX™ Ocular Pressure Adjusting Pump (OPAP). Participants age 22 or older, with or without pre-existing glaucoma, and who need routine cataract surgery within two months of providing informed consent were enrolled. Immediately prior to cataract surgery, the eye intended for surgery received NP application with the OPAP device while IOP was measured manometrically every 500 ms for approximately 30-second intervals throughout the following sequence: baseline IOP measurement recorded; -10 mm Hg of NP; NP stopped; -20 mmHg of NP; NP stopped. After the sequence, the OPAP was removed from the participant and cataract surgery proceeded as planned.

Results: 20 participants were enrolled. Three participants were excluded due to facial anatomy which precluded a stable seal with the OPAP goggles; thus 17 participants underwent the NP application sequence. The mean age was 70 years (range 55 to 84). 11 of 17 (64.7%) did not have a diagnosis of glaucoma. For the remaining six, three were “glaucoma suspects,” one had “mild POAG,” one had “mild normal-tension glaucoma,” and one had “severe POAG.” All eyes that received NP application had a dose-dependent decrease in IOP during NP application as measured with manometry, with normalization toward baseline IOP after NP was removed. Results are summarized in **Table 58** and **Figure 17**.

Previous studies evaluating the OPAP device have shown a decrease in IOP ranging from 40-60% of the applied NP; for example, application of -20 mm Hg of NP generally resulted in an IOP decrease of 8 to 12 mm Hg. The results of this study produced similar findings. The application of -10 mm Hg of NP resulted in a mean IOP decrease of 5.6 mmHg (33% change) and -20 mm Hg of NP resulted in mean IOP decrease of 8.0 mm Hg (51%). No participant demonstrated an increase in IOP during NP application. IOP reduction of 20% or more with respect to baseline IOP was noted for all participants. IOP returned to close to baseline following release of NP application. Three participants experienced “minor complications related to test

preparation procedures." One experienced a wound leak immediately post-operatively that was treated with wound rehydration and bandage contact lens placement; the wound leak was found to be resolved by the post-operative day 1 exam. Two participants were noted post-operatively to have small corneal epithelial defects in the operated eye; these were treated with bandage contact lens placement and were reported resolved at the post-operative week 1 visit.

9. Benefit- Risk Analysis

The sponsor is proposing this device for the following indications:

> "The FSYX™ Ocular Pressure Adjusting Pump (FSYX OPAP) is indicated as adjunctive therapy for the reduction of intraocular pressure during use in adult patients with open-angle glaucoma and IOP ≤ 21 mmHg."

FDA Commentary: *The excursion IOP methodology was devised by the sponsor to measure IOP while the device is in use (i.e., with negative pressure [NP] on), as the Goldmann applanator cannot be used while a patient is wearing the goggles. This parameter was found to be lowered only while the device is in use and the reduction ended once the device was turned off. The sponsor defines this alternative IOP parameter as TCPD relative to atmospheric pressure without accounting for the NP microenvironment. Although the data demonstrated that this alternative IOP parameter is lowered temporarily when the device is in use, TCPD relative to the applied NP in front of the eye actually increases by approximately 21.7% - 26.9% with device use. As a result, IOP defined in one way increases, while IOP defined in another way decreases.*

The Panel will be asked to assess benefit risk profile of the subject device for the proposed IFU statement with the current nomenclature and language.

In support of the subject De Novo, the sponsor provided data from the CP-X19 pivotal trial and 20 prior studies as listed in **Section 8** of the executive summary. In the CP-X19 pivotal trial, the following pre-specified primary and secondary effectiveness endpoints were met:

- 58.1% (54/93) of study eyes and 1.1% (1/93) of control eyes demonstrated a ≥20% reduction of IOP (by excursion tonometry) at the Week-52 clinic visit.
- 63.4% (59/93) of study eyes and 3.2% (3/93) of control eyes demonstrated a ≥20% reduction of IOP (by excursion tonometry) at the Week-52 sleep lab visit.

FDA Commentary: The pre-specified effectiveness endpoints on reduction of IOP were met. The Panel will be asked to comment on the clinical significance of IOP reduction via excursion tonometry.

In addition, at Week 52, mean IOP by Goldmann applanation tonometry (GAT) measured shortly prior to device use was 14.4 ± 2.8 mm Hg in study eyes and 14.0 ± 3.0 mm Hg in control eyes. After device use, mean IOP by GAT was 14.2 ± 3.0 mm Hg in study eyes and 14.0 ± 3.1 mm Hg in control eyes. The mean change in IOP by GAT was -0.3 ± 2.0 mm Hg in study eyes and 0.0 ± 2.2 in control eyes.

During the 1-year duration of the CP-X19 trial, 40 ocular AEs were reported involving 26 of 93 study eyes (28.0%) and 17 ocular AEs were reported involving 13 of 93 control eyes (14.0%). Comments and more detailed information related to the AEs relevant to discussion of device risks can be found in **Sections 7.5.2.1- 7.5.2.3** of this executive summary.

In the CP-X19 trial, *post hoc* analysis of visual field conducted by a third-party reading center revealed mean deviation worsening ≥2.5 dB in four study eyes (6.5%) at Weeks 26 and three study eyes (4.8%) at Week 52. In addition, optical coherence tomography (OCT) was collected from 62 participants at the Week 26 and Week 52 examinations, and was evaluated *post hoc* by a third-party reading center. No formal quantitative analysis of OCT data had been planned or was conducted.

FDA Commentary: *Glaucoma progression was not definitively detected or ruled out in the pivotal trial. The safety concern of possible "biomechanical insult" on the optic nerve head remains unclear.*

In CP-X19, the mean at-home wear time ranged from 5.44 to 5.63 hours nightly. Only eight participants (8.6%) used the device >7.5 hours nightly during one or more of the trial assessment intervals. Only three (3.2%) used the device >7.5 hours nightly during the majority of the trial intervals. It is unclear whether the rate of ocular adverse events would have been higher if more participants had used the device for the full eight hours of recommended wear time every night and if the attrition rate had been lower. In addition, the small proportion of participants able to achieve wear time longer than 7.5 hours nightly and the high dropout rate may indicate that device use may not be well-tolerated by patients. Furthermore, in Deficiency 4.c of the November 8 ***AINN letter*** *to the sponsor, the concern regarding possible harmful effects on health-related quality of life (HRQOL) and/or sleep disturbances was conveyed. The sponsor had stated in DENXXXXX2 that those with "device-related sleep disturbances can simply" stop using the device. Deficiency 4.c therefore requested that the sponsor verify that no other HRQOL data is available. In response, the sponsor stated that HRQOL data were collected only in the CP-X10 trial.*

The Panel will be asked to comment on whether the data supports a reasonable assurance of safety.

11. Tables

Table 1 (CP-X10): *Primary Effectiveness Endpoint at Day 90 Reduction of IOP (via Pneumotonometry) ≥ 20% during Application of Negative Pressure mITT Population*

Control Eye	Study Eye		
	Reduction < 20%	**Reduction ≥ 20%**	**Overall**
Reduction < 20%	12/64 (18.8%)	50/64 (78.1%)	62/64 (96.9%)
Reduction ≥ 20%	0/64 (0.0%)	2/64 (3.1%)	2/64 (3.1%)
Overall	12/64 (18.8%)	52/64 (81.3%)	64/64 (100.0%)
% Difference (Study % - Control %) = 81.3% - 3.1% = 78.1% **95% CI[1] of % Difference = 58.5%, 93.0%** **P-value[2] = <.001**			

[1] Bonett, D. G. and Price, R. M. (2012), Adjusted Wald Confidence Interval for a Difference of Binomial Proportions Based on Paired Data, J Educational and Behavioral Statistics, August 2012, Vol. 37, No. 4, pp. 479–488

[2] McNemar Test with a two-sided significance level of 0.05

Table 2 (CP-X10): *Primary Effectiveness Endpoint at Day 90 Reduction of IOP (via Pneumotonometry) ≥ 20% during Application of Negative Pressure Per Protocol Population*

Control Eye	Study Eye		
	Reduction < 20%	**Reduction ≥ 20%**	**Overall**
Reduction < 20%	6/58 (10.3%)	50/58 (86.2%)	56/58 (96.6%)
Reduction ≥ 20%	0/58 (0.0%)	2/58 (3.4%)	2/58 (3.4%)
Overall	6/58 (10.3%)	52/58 (89.7%)	58/58 (100.0%)
% Difference (Study % - Control %) = 89.7% - 3.4% = 86.2% **95% CI[1] of % Difference = 64.4%, 100.0%** **P-value[2] = <.001**			

[1] Bonett, D. G. and Price, R. M. (2012), Adjusted Wald Confidence Interval for a Difference of Binomial Proportions Based on Paired Data, J Educational and Behavioral Statistics, August 2012, Vol. 37, No. 4, pp. 479–488

[2] McNemar Test with a two-sided significance level of 0.05

Table 3 (CP-X10): *Best Corrected Distance Visual Acuity Safety Population*

BCDVA	Baseline		Day 90	
	Study n (%)	Control n (%)	Study n (%)	Control n (%)
N	64	64	58	58
20/20 or better	27 (42.2%)	30 (46.9%)	27 (46.6%)	30 (51.7%)
20/25 or better	42 (65.6%)	44 (68.8%)	49 (84.5%)	48 (82.8%)
20/32 or better	57 (89.1%)	53 (82.8%)	52 (89.7%)	52 (89.7%)
20/40 or better	59 (92.2%)	61 (95.3%)	57 (98.3%)	56 (96.6%)
Worse than 20/40 Better than 20/1000	5 (7.8%)	3 (4.7%)	1 (1.7%)	2 (3.4%)
Mean LogMAR Snellen Equivalent	0.053 20/22.6	0.044 20/22.1	0.032 20/21.5	0.027 20/21.3
SD	0.149	0.161	0.125	0.141
Not Reported	0	0	0	0
Total	64	64	58	58

N = number of available measurements. % = n/N × 100%.
Not Reported = Number of eyes with data not available at each visit.

Table 4 (CP-X10)*: Change in Best Corrected Distance Visual Acuity from Baseline Safety Population*

BCDVA	Day 90	
	Study n (%)	Control n (%)
N	58	58
Increase ≥ 15 letters	2 (3.4%)	2 (3.4%)
Increase 10-14 letters	4 (6.9%)	5 (8.6%)
Increase 5-9 letters	11 (19.0%)	7 (12.1%)
No change	32 (55.2%)	33 (56.9%)
Decrease 5-9 letters	8 (13.8%)	10 (17.2%)
Decrease 10-14 letters	0 (0.0%)	0 (0.0%)
Decrease ≥ 15 letters	1 (1.7%)	1 (1.7%)
Mean letter change	1.4	1.1
SD	6.0	6.4
Not Reported	0	0
Total	58	58

N = number of available measurements. % = n/N × 100%.
Not Reported = Number of eyes with data not available at each visit.

Table 5 (CP-X10): *Slit Lamp – Conjunctival Hyperemia Safety Population*

	Baseline n (%)	Day -7 n (%)	Day 0 n (%)	Day 30 n (%)	Day 60 n (%)	Day 90 n (%)
Study						
N	64	64	64	61	58	58
0	42 (65.6%)	42 (65.6%)	42 (65.6%)	42 (68.9%)	41 (70.7%)	44 (75.9%)
1+	20 (31.3%)	21 (32.8%)	21 (32.8%)	16 (26.2%)	16 (27.6%)	14 (24.1%)
2+	2 (3.1%)	1 (1.6%)	1 (1.6%)	3 (4.9%)	1 (1.7%)	0 (0.0%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	0	0	0
Total	64	64	64	61	58	58
Control						
N	64	64	64	61	58	58
0	42 (65.6%)	43 (67.2%)	42 (65.6%)	42 (68.9%)	44 (75.9%)	44 (75.9%)
1+	20 (31.3%)	20 (31.3%)	21 (32.8%)	17 (27.9%)	13 (22.4%)	14 (24.1%)
2+	2 (3.1%)	1 (1.6%)	1 (1.6%)	2 (3.3%)	1 (1.7%)	0 (0.0%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	0	0	0
Total	64	64	64	61	58	58

N = Number of eyes with non-missing values at each visit. % = n/N × 100%.
Not Reported = Number of eyes with data not available at each visit.
0 = None, 1+ = Trace, 2+ = Mild, 3+ = Moderate, 4+ = Severe

Table 6 (CP-X10): *Slit Lamp – Corneal Superficial Punctate Keratitis Safety Population*

	Baseline n (%)	Day -7 n (%)	Day 0 n (%)	Day 30 n (%)	Day 60 n (%)	Day 90 n (%)
Study						
N	64	64	64	61	58	58
0	54 (84.4%)	55 (85.9%)	48 (75.0%)	49 (80.3%)	49 (84.5%)	50 (86.2%)
1+	6 (9.4%)	6 (9.4%)	11 (17.2%)	6 (9.8%)	8 (13.8%)	8 (13.8%)
2+	3 (4.7%)	3 (4.7%)	5 (7.8%)	5 (8.2%)	1 (1.7%)	0 (0.0%)
3+	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	0	0	0
Total	64	64	64	61	58	58
Control						
N	64	64	64	61	58	58
0	53 (82.8%)	55 (85.9%)	48 (75.0%)	50 (82.0%)	50 (86.2%)	51 (87.9%)
1+	6 (9.4%)	7 (10.9%)	10 (15.6%)	6 (9.8%)	6 (10.3%)	5 (8.6%)
2+	5 (7.8%)	2 (3.1%)	6 (9.4%)	5 (8.2%)	2 (3.4%)	2 (3.4%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	0	0	0
Total	64	64	64	61	58	58

N = Number of eyes with non-missing values at each visit. % = n/N × 100%.
Not Reported = Number of eyes with data not available at each visit.
0 = None, 1+ = Trace, 2+ = Mild, 3+ = Moderate, 4+ = Severe

Table 7 (CP-X10): *Visual Field – Mean Deviation (MD) Safety Population*

Outcome	Baseline		Day 30		Day 90	
	Study	Control	Study	Control	Study	Control
N	64	64	61	61	58	58
Mean (SD)	-3.248 (4.072)	-3.120 (3.292)	-3.111 (4.571)	-3.280 (4.032)	-3.225 (4.679)	-2.897 (3.713)
1st Quartile	-5.020	-5.225	-3.850	-5.320	-5.500	-4.900
Median	-2.160	-2.425	-2.210	-2.130	-2.070	-1.915
3rd Quartile	-0.550	-0.465	-0.360	-0.340	-0.080	-0.140
Min, Max	-18.19, 2.64	-12.29, 2.87	-21.24, 3.15	-14.80, 1.88	-20.48, 2.33	-13.28, 2.25
Not Reported	0	0	0	0	0	0
Total	64	64	61	61	58	58
Change from Baseline			**n (%)**	**n (%)**	**n (%)**	**n (%)**
Improved ≥ 2.5 dB			7 (11.5%)	6 (9.8%)	4 (6.9%)	5 (8.6%)
Change < ±2.5 dB			49 (80.3%)	45 (73.8%)	48 (82.8%)	49 (84.5%)
Worsened ≥ 2.5 dB			5 (8.2%)	10 (16.4%)	6 (10.3%)	4 (6.9%)
Not Reported			0	0	0	0
Total			61	61	58	58

N = Number of eyes with non-missing values at each visit. % = n/N × 100%.
Not Reported = Number of eyes with data not available at each visit.

Table 8 (CP-X10)*: Visual Field – Pattern Standard Deviation (PSD) Safety Population*

Outcome	Baseline		Day 30		Day 90	
	Study	Control	Study	Control	Study	Control
N	64	64	61	61	58	58
Mean (SD)	3.109 (2.452)	3.585 (3.057)	3.186 (2.511)	3.385 (2.703)	2.962 (2.405)	3.057 (2.446)
1st Quartile	1.625	1.560	1.700	1.580	1.670	1.540
Median	1.910	2.125	2.130	2.300	1.975	1.955
3rd Quartile	3.670	4.195	3.320	3.990	3.060	3.930
Min, Max	1.13, 12.44	1.18, 14.43	1.18, 13.95	1.10, 13.31	1.02, 10.74	1.18, 13.78
Not Reported	0	0	0	0	0	0
Total	64	64	61	61	58	58

N = Number of eyes with non-missing values at each visit. % = n/N × 100%.
Not Reported = Number of eyes with data not available at each visit.

Table 9 (CP-X10): *GAT IOP Measurements Prior to versus Following Negative Pressure mITT Population*

	Baseline		Day 0		Day 30		Day 60		Day 90	
	Study	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**
GAT prior to Negative Pressure										
N	64	64	64	64	61	61	58	58	58	58
Mean	19.67	19.57	19.43	19.02	18.83	18.53	18.73	18.59	18.60	18.14
SD	3.55	3.72	3.45	3.68	3.22	3.65	4.07	3.92	3.73	3.31
Median	19.00	19.00	19.00	19.00	18.50	19.00	18.00	18.00	18.00	18.00
Minimum	13.50	13.00	13.50	11.00	14.00	11.00	12.00	12.00	12.00	11.00
Maximum	27.50	30.00	27.00	28.00	28.00	29.00	36.00	34.00	34.00	30.00
GAT following Negative Pressure										
N	64	64	64	64	61	61	58	58	58	58
Mean	18.33	18.20	17.79	18.01	17.63	17.82	17.41	17.53	17.51	17.21
SD	3.68	3.72	3.37	3.50	3.25	3.33	3.84	3.45	3.60	3.10
Median	18.00	18.00	17.25	17.50	17.50	18.00	17.00	17.00	17.50	17.00
Minimum	12.50	12.00	11.00	11.00	10.50	10.00	10.00	12.00	10.00	10.50
Maximum	28.00	28.00	26.00	27.00	25.00	26.00	32.00	28.50	29.00	27.00
Change in GAT from prior to vs following negative pressure										
N	64	64	64	64	61	61	58	58	58	58
Mean	-1.34	-1.37	-1.64	-1.01	-1.20	-0.72	-1.32	-1.06	-1.09	-0.94
SD	2.15	1.91	1.59	1.73	1.57	1.36	1.44	1.66	1.61	1.52
Median	-1.00	-1.50	-2.00	-1.00	-1.00	-1.00	-1.25	-1.00	-1.00	-1.00
Minimum	-7.00	-8.00	-6.00	-5.50	-5.00	-4.00	-4.00	-5.50	-5.00	-5.00
Maximum	4.50	2.50	2.00	3.00	2.00	3.00	1.00	4.00	2.00	3.50
Percent Change in GAT from prior to vs following negative pressure										
N	64	64	64	64	61	61	58	58	58	58
Mean	-6.6%	-6.7%	-8.3%	-4.8%	-6.2%	-3.5%	-6.8%	-5.1%	-5.7%	-4.8%
SD	10.5%	9.7%	7.9%	9.6%	8.5%	7.3%	7.6%	8.6%	8.5%	8.2%
Median	-5.7%	-6.7%	-9.1%	-4.7%	-7.1%	-4.3%	-6.3%	-5.3%	-6.6%	-5.3%
Minimum	-35.0%	-40.0%	-25.0%	-26.3%	-27.6%	-16.7%	-22.2%	-24.4%	-26.3%	-25.6%
Maximum	19.1%	10.6%	14.3%	27.3%	11.8%	21.4%	7.1%	26.7%	14.3%	20.6%

N = number of available measurements.

Table 10 (CP-X10): *Ocular Adverse Event Safety Population*

AE	Study Eyes N = 64			Control Eyes N = 64		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any reported ocular AEs	**29**	**19**	**29.7%**	**16**	**11**	**17.2%**
Loss of BCDVA ≥ 10 letters from baseline	2	2	3.1%	2	2	3.1%
Conjunctival chemosis (a worsening from baseline of ≥ 2 grades)	0	0	0.0%	0	0	0.0%
Conjunctival hyperemia (a worsening from baseline of ≥ 2 grades)	3	3	4.7%	3	3	4.7%
Conjunctival petechiae	0	0	0.0%	0	0	0.0%
Epithelial defect (due to use of the pneumatonometer or due to any other cause)	0	0	0.0%	0	0	0.0%
Eye pain	3	3	4.7%	0	0	0.0%
Lid edema (a worsening from baseline of ≥ 2 grades)	11	11	17.2%	5	5	7.8%
Lid erythema (a worsening from baseline of ≥ 2 grades)	1	1	1.6%	1	1	1.6%
Symptoms and signs of dry eye (e.g. a worsening from baseline of ≥ 2 grades in SPK)	5	4	6.3%	3	3	4.7%
Other						
Blepharitis	1	1	1.6%	1	1	1.6%
Epiphora	2	2	3.1%	1	1	1.6%
Inflamed pterygium	1	1	1.6%	0	0	0.0%

% = n/N × 100%.
An eye could report with multiple events.
None of the AEs were serious.

Table 11 (CP-X10)*: Periorbital Adverse Event Safety Population*

AE	Study Eyes N = 64			Control Eyes N = 64		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any reported periorbital AEs	**13**	**12**	**18.8%**	**11**	**9**	**14.1%**
Periorbital contact dermatitis	1	1	1.6%	1	1	1.6%
Periorbital ecchymosis	0	0	0.0%	0	0	0.0%
Periorbital pain	1	1	1.6%	1	1	1.6%
Other						
Periorbital edema	9	9	14.1%	7	7	10.9%
Periorbital erythema	1	1	1.6%	1	1	1.6%
Periorbital skin sensitivity	1	1	1.6%	1	1	1.6%

% = n/N × 100%.
An eye could report with multiple events.

***Table 12 (CP-X10)**: Reported Ocular and Periorbital Adverse Event by Severity Safety Population*

AE	Study Eyes N = 64			Control Eyes N = 64		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Ocular AEs						
Loss of BCDVA ≥ 10 letters from baseline	2 (3.1%)	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)
Conjunctival hyperemia (a worsening from baseline of ≥ 2 grades)	3 (4.7%)	0 (0.0%)	0 (0.0%)	3 (4.7%)	0 (0.0%)	0 (0.0%)
Eye pain	2 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lid edema (a worsening from baseline of ≥ 2 grades)	5 (7.8%)	6 (9.4%)	0 (0.0%)	4 (6.3%)	1 (1.6%)	0 (0.0%)
Lid erythema (a worsening from baseline of ≥ 2 grades)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Symptoms and signs of dry eye (e.g. a worsening from baseline of ≥ 2 grades in SPK)	2 (3.1%)	2 (3.1%)	0 (0.0%)	2 (3.1%)	1 (1.6%)	0 (0.0%)
Other						
Blepharitis	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Epiphora	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Inflamed pterygium	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Periorbital AEs						
Periorbital contact dermatitis	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Periorbital pain	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Other						
Periorbital edema	3 (4.7%)	6 (9.4%)	0 (0.0%)	5 (7.8%)	2 (3.1%)	0 (0.0%)
Periorbital erythema	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Periorbital skin sensitivity	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)

Maximum severity of the event was used for eyes with multiple reports of the same event.
% = n/N × 100%.

Table 13 (CP-X10): *Device-Related Ocular and Periorbital Adverse Event Safety Population*

AE	Study Eyes N = 64			Control Eyes N = 64		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any reported device-related ocular and periorbital AEs	**33**	**22**	**34.4%**	**21**	**15**	**23.4%**
Ocular AEs	**20**	**14**	**21.9%**	**10**	**9**	**14.1%**
Loss of BCDVA ≥ 10 letters from baseline	0	0	0.0%	1	1	1.6%
Eye pain	3	3	4.7%	0	0	0.0%
Lid edema (a worsening from baseline of ≥ 2 grades)	11	11	17.2%	5	5	7.8%
Symptoms and signs of dry eye (e.g. a worsening from baseline of ≥ 2 grades in SPK)	4	3	4.7%	3	3	4.7%
Other						
Epiphora	2	2	3.1%	1	1	1.6%
Periorbital AEs	**13**	**12**	**18.8%**	**11**	**9**	**14.1%**
Periorbital contact dermatitis	1	1	1.6%	1	1	1.6%
Periorbital pain	1	1	1.6%	1	1	1.6%
Other						
Periorbital edema	9	9	14.1%	7	7	10.9%
Periorbital erythema	1	1	1.6%	1	1	1.6%
Periorbital skin sensitivity	1	1	1.6%	1	1	1.6%

% = n/N × 100%.
An eye could report with multiple events.

Table 14 (CP-X10): *Non-Ocular Adverse Event Safety Population*

AE	N = 64 Subjects		
	# of Reports	# of Subjects	% of Subjects
Any reported non-ocular AEs	**18**	**14**	**21.9%**
Anal papillae	1	1	1.6%
Brow ecchymosis	1	1	1.6%
Difficulty sleeping	1	1	1.6%
Diverticulosis	1	1	1.6%
Headache (e.g., tension, migraine, sinus, etc.)	8	7	10.9%
Paronychia, right thumb	1	1	1.6%
Psychiatric admission > 24 hours*	1	1	1.6%
Scalp numbness, intermittent	1	1	1.6%
Shingles	1	1	1.6%
Urinary Tract Infection*	1	1	1.6%
Wrinkle at brow	1	1	1.6%

% = n/N × 100%.
A subject could report with multiple events.
* Serious AE

***Table 15 (CP-X10)**: Symptoms and Health Problems Checklist–18 (SHPC–18) Local Eye Symptoms Safety Population*

Symptom	Study Eye		Control Eye	
	Baseline n (%)	Day 90 n (%)	Baseline n (%)	Day 90 n (%)
Total	64	58	64	58
Missed Assessment	0	0	0	0
Eye irritation or burning, N	**64**	**58**	**64**	**58**
No	54 (84.4%)	53 (91.4%)	54 (84.4%)	54 (93.1%)
Yes	10 (15.6%)	5 (8.6%)	10 (15.6%)	4 (6.9%)
Not at all	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
A little	7 (70.0%)	3 (60.0%)	8 (80.0%)	3 (75.0%)
Somewhat	2 (20.0%)	2 (40.0%)	2 (20.0%)	1 (25.0%)
A moderate amount	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
A lot	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Feeling like something is in your eye(s), N	**64**	**58**	**64**	**58**
No	55 (85.9%)	47 (81.0%)	56 (87.5%)	49 (84.5%)
Yes	9 (14.1%)	11 (19.0%)	8 (12.5%)	9 (15.5%)
Not at all	0 (0.0%)	1 (9.1%)	2 (25.0%)	4 (44.4%)
A little	6 (66.7%)	7 (63.6%)	4 (50.0%)	3 (33.3%)
Somewhat	1 (11.1%)	3 (27.3%)	1 (12.5%)	2 (22.2%)
A moderate amount	1 (11.1%)	0 (0.0%)	1 (12.5%)	0 (0.0%)
A lot	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Droopy eyelids, N	**64**	**58**	**64**	**58**
No	58 (90.6%)	47 (81.0%)	58 (90.6%)	51 (87.9%)
Yes	6 (9.4%)	11 (19.0%)	6 (9.4%)	7 (12.1%)
Not at all	0 (0.0%)	1 (9.1%)	0 (0.0%)	4 (57.1%)
A little	5 (83.3%)	3 (27.3%)	5 (83.3%)	1 (14.3%)
Somewhat	1 (16.7%)	3 (27.3%)	1 (16.7%)	0 (0.0%)
A moderate amount	0 (0.0%)	2 (18.2%)	0 (0.0%)	1 (14.3%)
A lot	0 (0.0%)	2 (18.2%)	0 (0.0%)	1 (14.3%)
Excessive tearing, N	**64**	**58**	**64**	**58**
No	56 (87.5%)	48 (82.8%)	57 (89.1%)	50 (86.2%)
Yes	8 (12.5%)	10 (17.2%)	7 (10.9%)	8 (13.8%)
Not at all	0 (0.0%)	1 (10.0%)	1 (14.3%)	1 (12.5%)
A little	4 (50.0%)	5 (50.0%)	4 (57.1%)	4 (50.0%)
Somewhat	0 (0.0%)	2 (20.0%)	0 (0.0%)	1 (12.5%)
A moderate amount	4 (50.0%)	2 (20.0%)	2 (28.6%)	2 (25.0%)
A lot	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = number of available subjects with non-missing Yes/No response.
N < total number of subjects with assessment means missing response for the corresponding SHPC-18 symptom questionnaire.
% = n/N × 100%.

Symptom	Study Eye		Control Eye	
	Baseline n (%)	Day 90 n (%)	Baseline n (%)	Day 90 n (%)
Skin sensitivity around your eye(s), N	**64**	**58**	**64**	**58**
No	62 (96.9%)	45 (77.6%)	62 (96.9%)	46 (79.3%)
Yes	2 (3.1%)	13 (22.4%)	2 (3.1%)	12 (20.7%)
Not at all	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (41.7%)
A little	1 (50.0%)	9 (69.2%)	1 (50.0%)	5 (41.7%)
Somewhat	0 (0.0%)	3 (23.1%)	0 (0.0%)	2 (16.7%)
A moderate amount	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
A lot	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
Eye pain, N	**64**	**58**	**64**	**58**
No	60 (93.8%)	54 (93.1%)	61 (95.3%)	56 (96.6%)
Yes	4 (6.3%)	4 (6.9%)	3 (4.7%)	2 (3.4%)
Not at all	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (50.0%)
A little	2 (50.0%)	2 (50.0%)	1 (33.3%)	0 (0.0%)
Somewhat	1 (25.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
A moderate amount	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)
A lot	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Red eye(s), N	**64**	**58**	**64**	**58**
No	43 (67.2%)	47 (81.0%)	45 (70.3%)	48 (82.8%)
Yes	21 (32.8%)	11 (19.0%)	19 (29.7%)	10 (17.2%)
Not at all	2 (9.5%)	1 (9.1%)	3 (15.8%)	2 (20.0%)
A little	10 (47.6%)	7 (63.6%)	9 (47.4%)	5 (50.0%)
Somewhat	6 (28.6%)	1 (9.1%)	5 (26.3%)	1 (10.0%)
A moderate amount	3 (14.3%)	0 (0.0%)	2 (10.5%)	1 (10.0%)
A lot	0 (0.0%)	2 (18.2%)	0 (0.0%)	1 (10.0%)

N = number of available subjects with non-missing Yes/No response.
N < total number of subjects with assessment means missing response for the corresponding SHPC-18 symptom questionnaire.
% = n/N × 100%.

***Table 16 (CP-X19)**: Schedule of Study Treatments and Clinical Assessments*

Procedures	Baseline Visit 1 (Day -14)	Baseline Visit 1a[1] (~Day – 44)	Visit 2 (Day -7) ± 1 day	Visit 3^ (Day 0) - 3/+ 7 days	Visit 4 (Wk 6) ± 14 days	Visit 5 (Wk 12) ± 14 days	Visit 6 (Wk 26) ± 28 days	Visit 7 (Wk 38) ± 28 days	Visit 8^ (Wk 52) ± 28 days
Informed Consent	X								
Ocular Medical History	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Eligibility Assessment	X	X	X	X					
Completion of 30-day washout		X							
CDVA				X	X	X	X	X	
Manifest Refraction	X			X†	X†	X†	X†	X†	X
BCDVA (ETDRS)	X			X†	X†	X†	X†	X†	X
Slit Lamp Exam	X		X	X	X	X	X	X	X
Gonioscopy	X†								
Dilated Fundus Exam	X†								X
OCT of ONH and RNFL[1]	X						X‡		X‡
Central Corneal Thickness	X†								
Visual Field (24-2 SITA Standard)[1]	X†						X‡,¶		X‡,¶
Goggle Fit Check[§]	X#	X		X	X	X	X	X	
OPAP Goggle Replacement				X	X	X	X	X	
GAT*	X	X		X	X	X	X	X	X
Model 30 Pneumatonometry*	X#	X		X			X		X
Program/Re-program Pump	OD/OS#	OD/OS	OD/OS	SE	O	O	O	O	
Pump data download			X	X	X	X	X	X	X
Subject Training on OPAP Operation and Wear	X	X							
Adverse Events	X	X	X	X	X	X	X	X	X
Randomization				X					
Sleep Lab – supine IOP measurements via Model 30 pneumatonometry at 11:00 pm, 2:00 am, and 5:00 am*				X					X

OD=right eye; OS=left eye; SE= study eye. All procedures performed OU with the goggles OFF unless otherwise specified.

[1] Visit 1a is for subjects who used ocular hypotensive medication at Visit 1. These subjects were required to undergo a minimum 30-day medication washout, then return for additional screening assessments at Visit 1a.

***Table 17 (CP-X19)**: Pump Programming Parameters for In-Clinic IOP Measurement During Negative Pressure Application and Home Use*

Study Visit	Pump Programming Used			Study Eye	Control Eye
	In-Clinic IOP Measurement during NP Application	Subsequent Home Use			
Visit 1 (D -14)	Reference IOP of 6 mmHg	- 5 mmHg		X	X
Visit 2 (D -7)	N/A	IOP from Visit 1	Pump Program	X	X
		≤ 11 mmHg	- 5 mmHg		
		12 mmHg	- 6 mmHg		
		13-14 mmHg	- 7 mmHg		
		15-16 mmHg	- 8 mmHg		
		17-18 mmHg	- 9 mmHg		
		19-20 mmHg	- 10 mmHg		
		21-22 mmHg	- 11 mmHg		
		> 22 mmHg	- 12 mmHg		

Study Visit	Pump Programming Used		Study Eye	Control Eye
	In-Clinic IOP Measurement during NP Application	Subsequent Home Use		
Visit 3 (Day 0)	Reference IOP of 6 mmHg (seated)	Reference IOP of 6 mmHg (seated) or adjusted investigator prescription	X	0
Initial Sleep Lab (≤ Day 21)	Reference IOP of 6 mmHg (supine) if different from Visit 3	Reference IOP of 6 mmHg (supine) if different from Visit 3	X	0
Visit 4 (Wk 6)	N/A	N/A or adjusted investigator prescription*	X	0
Visit 5 (Wk 12)	N/A	N/A or adjusted investigator prescription*	X	0
Visit 6 (Wk 26)	Settings from previous home use period	N/A or adjusted investigator prescription*	X	0
Visit 7 (Wk 38)	N/A	N/A or adjusted investigator prescription*	X	0
Final Sleep Lab (prior to Wk 52)	Settings from prior period of home use	Maintain settings from prior period of home use	X	0
Visit 8 (Wk 52)	Settings from prior period of home use	N/A	N/A	N/A

*A reference IOP of 6 mmHg (measured via pneumotonometry) was used for NP programming. Pumps could not be set to reference IOP < 6 mmHg.

***Table 18 (CP-X19)**: Analysis Populations*

Population	Statistics n (%)
ITT Population[1]	94 (100%)
mITT Population[2]	93 (98.9%)
Safety Population[4]	93 (98.9%)
Per Protocol Population[3]	60 (63.8%)

% = n/N × 100%. N = total number of randomized subjects.

1 The ITT Population is all randomized subjects.

2 The mITT Population is all randomized subjects who had at least one full application of NP (defined as a minimum of 20 minutes of NP application in the home use setting) to the study eye after randomization (between Visit 3 and Visit 8).

3 The Per Protocol Population is all subjects in the mITT population who met all entry criteria, had no major protocol deviations, and completed their Week 52 visits (both in-clinic and the sleep lab).

4 The Safety population is all subjects who had at least one application (of any duration) of NP after randomization.

***Table 19 (CP-X19)**: Subject Accountability (mITT Population)*

	Visit 3 (Day 0)	Initial Sleep Lab (≤ Day 21)	Visit 4 (Wk 6)	Visit 5 (Wk 12)	Visit 6 (W 26)	Visit 7 (Wk 38)	Final Sleep Lab	Visit 8 (Wk 52)
Available for analysis[1]	93 (100.0%)	80 (86.0%)	81 (87.1%)	74 (79.6%)	68 (73.1%)	65 (69.9%)	62 (66.7%)	62 (66.7%)
Missing	0 (0.0%)	13 (14.0%)	12 (12.9%)	19 (20.4%)	25 (26.9%)	28 (30.1%)	31 (33.3%)	31 (33.3%)
Discontinued	0 (0.0%)	6 (6.5%)	12 (12.9%)	19 (20.4%)	25 (26.9%)	28 (30.1%)	31 (33.3%)	31 (33.3%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up[2]	0 (0.0%)	6 (6.5%)	12 (12.9%)	19 (20.4%)	25 (26.9%)	28 (30.1%)	31 (33.3%)	31 (33.3%)
Missed visit[3]	0 (0.0%)	7 (7.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Active[4]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
% Accountability[5]	93/93 (100.0%)	80/80 (100.0%)	81/81 (100.0%)	74/74 (100.0%	68/68 (100.0%	65/65 (100.0%	62/62 (100.0%	62/62 (100.0%)

[1] The mITT Population consists of all randomized subjects who had at least one full application (minimum of 20 minutes in home use setting) of NP to the study eye between Visit 3 and Visit 8. All but 1 of the 94 subjects randomized received at least one full NP application; therefore, the mITT population consisted of 93 subjects (1 subject, after randomization on Day 0, had GAT IOP measurement > 21 mmHg and was discontinued prior to NP application).

[2] Lost to follow-up includes withdrawal of consent, investigator decision, and reasons other than death

[3] Missed Visit = not examined at the scheduled visit, but may be seen at a subsequent visit

[4] Active = not yet seen or not yet eligible for the interval

[5] % Accountability [available for analysis/(enrolled – discontinued – active)] x 100

***Table 20 (CP-X19)**: Demographics (mITT Population)*

Age at Consent	**(Years)**
N	93
Mean ± SD	62.4 ± 10.7
1st Quartile	54
Median	61
3rd Quartile	70
Min, Max	40, 85
Missing	0
	n (%)
Gender	
Male	30 (32.3%)
Female	63 (67.7%)
Race	
White	64 (68.8%)
Black/African American	13 (14.0%)
American Indian/Alaskan Native	0 (0.0%)
Asian	15 (16.1%)
Native Hawaiian/Pacific Islander	0 (0.0%)
Other*	1 (1.1%)
Ethnicity	
Hispanic or Latino	18 (19.4%)
Not Hispanic and not Latino	75 (80.6%)
Study Eye	
OD	46 (49.5%)
OS	47 (50.5%)

% = n/N × 100%.

* Mestizo

***Table 21 (CP-X19)**: Demographics (PP Population)*

Age at Consent	**(Years)**
N	60
Mean ± SD	61.4 ± 10.6
1st Quartile	53.8
Median	61
3rd Quartile	69.3
Min, Max	40, 81
Missing	0
	n (%)
Gender	
Male	21 (35.0%)
Female	39 (65.0%)
Race	
White	44 (73.3%)
Black/African American	9 (15.0%)
American Indian/Alaskan Native	0 (0.0%)
Asian	7 (11.7%)
Native Hawaiian/Pacific Islander	0 (0.0%)
Other	0 (0.0%)
Ethnicity	
Hispanic or Latino	13 (21.7%)
Not Hispanic and not Latino	47 (78.3%)
Study Eye	
OD	32 (53.3%)
OS	28 (46.7%)

% = n/N × 100%.

***Table 22 (CP-X19)**: Baseline (Day -14) Characteristics (mITT Population)*

Characteristic	Study Eye (n = 93) n (%)	Control Eye (n = 93) n (%)
Topical Ocular Hypotensive Medications*		
0	41 (44.1%)	43 (46.2%)
1	35 (37.6%)	35 (37.6%)
2	10 (10.8%)	10 (10.8%)
3	5 (5.4%)	3 (3.2%)
4	2 (2.2%)	2 (2.2%)
BCDVA at Baseline (LogMAR)		
Mean (Snellen)	0.06 (20/23.1)	0.08 (20/23.8)
Standard Deviation	0.12	0.14
Median (Snellen)	0.02 (20/20.9)	0.04 (20/21.9)
Minimum (Snellen)	-0.18 (20/13.2)	-0.2 (20/12.6)
Maximum (Snellen)	0.64 (20/87.3)	0.9 (20/158.9)
Manifest Refraction Spherical Equivalent		
Mean	-1.0	-1.4
Standard Deviation	2.5	2.7
Median	-0.25	-0.5
Minimum	-8.75	-9.75
Maximum	4.75	3.75
Baseline IOP (GAT) (mmHg)		
Mean	14.7	14.8
Standard Deviation	2.0	2.2
Median	14	14
Minimum	12	12
Maximum	20	21
Central Corneal Thickness (µm)		
Mean	536.2	538.1
Standard Deviation	38.2	37.5
Median	543	542
Minimum	413	440
Maximum	640	620
Gonioscopy Shaffer Grade		
Superior-Temporal (ST) Quadrant		
0 - II	0 (0.0%)	0 (0.0%)
III - IV	93 (100.0%)	93 (100.0%)
Superior-Nasal (SN) Quadrant		
0 - II	0 (0.0%)	0 (0.0%)
III - IV	93 (100.0%)	93 (100.0%)
Inferior-Temporal (IT) Quadrant		
0 - II	0 (0.0%)	0 (0.0%)

Table 23 (CP-X19): *Summary of All Protocol Deviations*

Deviation Type	Number of Deviations n
Major Protocol Deviations	**3**
Control eye received NP after randomization	1
Incomplete Excursion sequence at Week 52 Sleep Lab	1
Incomplete Excursion sequence at Week 52 Clinic	1
Minor Protocol Deviations	**124**
Missed assessment	13
Assessment out of visit window	1
Assessment performed incorrectly	
• Required 3rd IOP measurement not obtained	4
• Additional 3rd IOP measurement obtained but not required	5
• Examination completed but not recorded	1
Incorrect NP value programmed	
• Overprogrammed: Pre-Randomization adaptation period	23
• Underprogrammed: Pre-Randomization adaptation period	17
• Overprogrammed: Post-Randomization	5
• Under programmed Post-Randomization	2
Device (goggles) not dispensed per protocol	10
Incomplete informed consent process	11
Incorrect version of consent form used	3
Subject failed to reconsent	16
Missed Visit	13
Total Deviations	**127**

Table 24 (CP-X19): *Summary of All Protocol Deviations (Including Number of Subjects Affected)*

Deviation Type	Number of Deviations	Number of Subjects Affected
Major Protocol Deviations	**3**	**2**
Control eye received NP after randomization	1	1
Incomplete Excursion sequence at Week 52 Sleep Lab	1	1
Incomplete Excursion sequence at Week 52 Clinic	1	1
Minor Protocol Deviations	**124**	**42**
Missed assessment	13	11
Assessment out of window	1	1
Assessment performed incorrectly	10	9
Required 3rd IOP measurement not obtained	3	3
Additional 3rd IOP measurement obtained but not required	6	6
Examination completed but not recorded	1	1
Incorrect NP value programmed	47	36
Overprogrammed: Pre-randomization adaptation period	23	20
Underprogrammed: Pre-randomization adaptation period	17	15
Overprogrammed: Post-randomization	5	2
Underprogrammed Post-randomization	2	2
Device (goggles) not dispensed per protocol	10	6
Incomplete informed consent process	11	6
Incorrect version of consent form used	3	3
Subject failed to consent	16	9
Missed visit	13	13

Table 25 (CP-X19)*: Listing of Subjects for Whom a Study-Required Assessment was Missed (n=13)*

Subject ID	Visit	Assessment Missed
(b)(6)	Visit 2: Day -7	Slit lamp exam
	Visit 6 Sleep Lab[1]: Week 26	Masked IOP and Excursion testing
	Post Visit 8: Week 52	Post-exit visit visual field and OCT
	Visit 6: Week 26	OCT
	Visit 6: Week 26	OCT
	Visit 4: Week 6	BCDVA
	Visit 5: Week 12	BCDVA
	Visit 3: Day 0	BCDVA
	Visit 1: Day -14	Excursion testing
	Visit 6 Sleep Lab[1]: Week 26	Masked IOP and Excursion testing
	Visit 8 Sleep Lab: Week 52	Masked IOP and Excursion testing (subject uncooperative)
	Visit 8 Week 52	Masked IOP and Excursion testing (subject uncooperative)
	Visit 7: Week 38	BCDVA

[1] The Visit 6 Sleep Lab requirement was removed from the study protocol CP-(b)19, Revision 6, dated 10 Nov 2021.

***Table 26 (CP-X19)**: Negative Pressure Settings for Subsequent Home Use (mITT Population)*

	Day 0		Week 6		Week 12		Week 26		Week 38	
	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control
Programmed NP, N	93	93	81	81	74	74	68	68	65	65
Mean	10.0	0.0	12.0	0.0	12.1	0.0	11.7	0.0	11.9	0.0
SD	2.4	0.0	3.1	0.0	3.0	0.0	3.1	0.0	3.8	0.0
1st Quartile	8.0	0.0	10.0	0.0	10.0	0.0	10.0	0.0	10.0	0.0
Median	10.0	0.0	12.0	0.0	12.0	0.0	12.0	0.0	11.0	0.0
3rd Quartile	11.0	0.0	14.0	0.0	14.0	0.0	14.0	0.0	14.0	0.0
Minimum	5.0	0.0	6.0	0.0	6.0	0.0	5.0	0.0	5.0	0.0
Maximum	16.0	0.0	20.0	0.0	20.0	0.0	20.0	0.0	20.0	0.0
Not Reported	0	0	0	0	0	0	0	0	0	0
Total	93	93	81	81	74	74	68	68	65	65
Programmed NP Change from Day 0, N	--	--	81	81	74	74	68	68	65	65
Mean	--	--	2.0	0.0	2.0	0.0	1.6	0.0	1.8	0.0
SD	--	--	2.9	0.0	2.8	0.0	3.2	0.0	4.0	0.0
1st Quartile	--	--	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Median	--	--	2.0	0.0	2.0	0.0	1.5	0.0	1.0	0.0
3rd Quartile	--	--	4.0	0.0	4.0	0.0	4.0	0.0	4.0	0.0
Minimum	--	--	-6.0	0.0	-6.0	0.0	-8.0	0.0	-8.0	0.0
Maximum	--	--	9.0	0.0	9.0	0.0	9.0	0.0	12.0	0.0
Not Reported	--	--	0	0	0	0	0	0	0	0
Total	--	--	81	81	74	74	68	68	65	65

***Table 27 (CP-X19)**: Negative Pressure Settings for Subsequent Home Use (PP Population)*

	Day 0		Week 6		Week 12		Week 26		Week 38	
	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control
Programmed NP, N	60	60	60	60	60	60	60	60	60	60
Mean	10.1	0.0	12.2	0.0	12.0	0.0	11.7	0.0	12.1	0.0
SD	2.4	0.0	3.0	0.0	3.0	0.0	3.1	0.0	3.8	0.0
1st Quartile	8.0	0.0	10.0	0.0	10.0	0.0	10.0	0.0	10.0	0.0
Median	10.0	0.0	12.0	0.0	12.0	0.0	12.0	0.0	11.5	0.0
3rd Quartile	11.0	0.0	14.0	0.0	14.0	0.0	14.0	0.0	14.3	0.0
Minimum	6.0	0.0	6.0	0.0	6.0	0.0	5.0	0.0	5.0	0.0
Maximum	16.0	0.0	20.0	0.0	20.0	0.0	20.0	0.0	20.0	0.0
Not Reported	0	0	0	0	0	0	0	0	0	0
Total	60	60	60	60	60	60	60	60	60	60
Programmed NP Change from Day 0, N			60	60	60	60	60	60	60	60
Mean			2.1	0.0	2.0	0.0	1.7	0.0	2.0	0.0
SD			3.0	0.0	2.9	0.0	3.2	0.0	4.0	0.0
1st Quartile			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Median			2.0	0.0	2.0	0.0	2.0	0.0	1.0	0.0
3rd Quartile			4.0	0.0	4.0	0.0	4.0	0.0	4.0	0.0
Minimum			-6.0	0.0	-6.0	0.0	-8.0	0.0	-8.0	0.0
Maximum			9.0	0.0	9.0	0.0	9.0	0.0	12.0	0.0
Not Reported			0	0	0	0	0	0	0	0
Total			60	60	60	60	60	60	60	60

***Table 28 (CP-X19)**: Summary of Subjects Who Received Negative Pressure Application > -12 mmHg and Completed Study (mITT Population)*

Subject ID:	NP Setting (mmHg)					Min – Max Wear Time (Hr)	Device-Related AE
	Day 0 In-Clinic	Initial Sleep Lab	Wk 26	Wk 52 Sleep Lab	Wk 52 In-Clinic		
(b)(6)	-9	-13	-13	-13	-13	5.3 – 6.0	Yes
	-11	-11	-13	-13	-13	4.6 – 6.1	Yes
	-8	-15	-16*	-14	-14	2.0 – 4.7	Yes
	-10	-16	-15	-15	-15	6.6 – 7.7	Yes
	-12	-14	-14	-14	-14	4.0 – 6.1	Yes
	-11	-15	-16*	-16	-16	5.4 – 6.2	
	-10	-14	-14	-14	-14	3.6 – 6.1	
	-6	-16	-19*	-19	-19	2.5 – 3.9	Yes
	-9	-17	-15	-15	-15	4.9 – 7.9	Yes
	-13	-14	-14	-14	-14	5.3 – 6.2	
	-10	-15	-13	-13	-13	5.8 – 6.2	Yes
	-16	-20	-20	-20	-20	5.5 – 6.5	
	-16	-16	-16	-16	-16	3.6 – 6.3	Yes
	-15	-14	-14	-14	-14	4.5 – 4.9	
	-15	-16	-16	-16	-16	6.0 – 6.8	
	-10	-19	-19	-19	-19	3.7 – 5.3	
	-9	-15	-15	-15	-15	6.1 – 7.0	Yes
	-8	-13	-13	-13	-13	7.4 – 7.7	Yes
	-10	-14	-14	-14	-14	7.0 – 7.5	
	-12	-16	-16	-16	-16	3.2 – 5.1	
	-10	-16	-16	-16	-16	6.3 – 6.6	Yes
	-13	-13	-13	-13	-13	5.9 – 6.4	
	-8	-15	-15	-15	-15	5.0 – 6.4	
	-10	-14	-17*	-13	-13	5.3 – 6.2	
	-10	-10	-16*	-16	-16	6.0 – 6.8	Yes
	-14	-14	-14	-14	-14	4.9 – 7.3	
	-8	-8	-16*	-16	-16	5.9 – 6.1	
	-11	-20	-14	-14	-14	4.7 – 5.8	
	-14	-14	-14	-14	-14	6.5 – 8.3	Yes
	-11	-13	-13	-13	-13	6.3 – 7.0	
	-11	-17	-18*	-18	-18	2.0 – 2.8	Yes
	-10	-13	-14*	-14	-14	3.6 – 5.0	
	-7	-14	-17*	-17	-17	5.3 – 6.0	
	-8	-14	-20*	-20	-20	7.0 – 7.8	
	-10	-15	-17*	-17	-17	5.5 – 6.7	Yes
	-11	-18	-20*	-20	-20	5.4 – 6.2	

Subject ID:	NP Setting (mmHg)					Min – Max Wear Time (Hr)	Device-Related AE
	Day 0 In-Clinic	Initial Sleep Lab	Wk 26	Wk 52 Sleep Lab	Wk 52 In-Clinic		
(b)(6)	-11	-15	-19*	-19	-19	6.0 – 6.3	Yes
	-11	-13	-14*	-14	-14	5.8 – 6.9	Yes

AE=adverse event; mITT=Modified Intent to Treat; NP=negative pressure; Wk=week.
*Week 26 NP adjustment was made based on mean IOP (supine) from an interim sleep lab.

***Table 29 (CP-X19)**: Summary of Subjects Who Received Negative Pressure Application > -12 mmHg and Discontinued Study (mITT Population)*

Subject ID:	NP Setting (mmHg)		Discontinuation Days Post-Randomization	Min – Max Wear Time (Hr)	Device-Related AE
	Day 0 In-Clinic	Initial Sleep Lab			
(b)(6)	-8	-13	190	2.4 – 2.7	
	-9	-14	367	3.0 – 4.6	Yes
	-10	-14	164	3.3 – 4.6	Yes
	-13	-13	161	3.4 – 3.8	
	-14	-14	244	1.0 – 6.2	
	-14	-14	9	Not recorded	
	-13	-13	265	6.2 – 7.9	
	-10	-14	80	5.1 – 5.7	
	-6	-13	90	5.8 – 6.1	
	-9	-13	35	Not recorded	
	-14	-16	336	2.3 – 3.7	
	-9	-15	125	3.0 – 3.1	Yes
	-14	-19	11	Not recorded	
	-11	-17	363	4.3 – 4.3	Yes
	-10	-15	15	Not recorded	Yes

AE=adverse event; Hr=hours; NP=negative pressure.

***Table 30 (CP-X19)**: Ocular Pressure Adjusting Pump Home Use (mITT Population)*

Visit Interval	Day 0 to Week 6	Week 6 to Week 12	Week 12 to Week 26	Week 26 to Week 38	Week 38 to Week 52
Nominal visit interval (days)	**42**	**42**	**98**	**84**	**98**
Days of OPAP use during the visit interval*					
Average days between visits	37.73	43.76	87.10	84.95	101.61
N	81	74	68	65	62
Mean	32.95	37.49	71.59	66.43	79.79
SD	8.87	11.43	19.82	23.10	23.17
1st Quartile	26.00	30.00	61.00	54.00	66.00
Median	31.00	38.50	72.00	68.00	79.00
3rd Quartile	40.00	45.00	85.00	80.00	96.00
Minimum	14.00	8.00	5.00	2.00	20.00
Maximum	56.00	63.00	112.00	132.00	126.00
Average daily wear (in hours) of OPAP use during the visit interval#					
N	81	74	68	65	62
Mean	5.52	5.44	5.52	5.52	5.63
SD	1.22	1.42	1.55	1.43	1.33
1st Quartile	4.65	4.79	4.58	4.58	4.90
Median	5.83	5.77	5.91	5.93	5.85
3rd Quartile	6.38	6.40	6.43	6.39	6.34
Minimum	2.71	2.01	1.01	2.05	2.02
Maximum[1]	7.65	7.82	8.92	8.98	8.34

*Days where treatment was dispensed for more than 20min.
#Sum of the usage of ONLY the days above 20min (any usage less than 20min is considered ZERO, and its corresponding day is not considered a usage day), divided by "Days of MPD use during the visit interval", divided by 3600 seconds, then converted into hours
[1] This statistic includes subjects who restarted treatment after an 8-hour treatment cycle was completed.

***Table 31 (CP-X19)**: IOP Changes during Sleep Lab Visits compared to In-Clinic, by Response Category and Eye, at Weeks 0 and 52, in Study CP-X19 (mITT Population)*

Visit, n (%):	IOP Difference Category	Study Eye	Control Eye	All Eyes
Initial (Day 0) Sleep Lab (N=80)	< -2 mmHg	1 (1.3%)	6 (7.5%)	7 (4.4%)
	-2 to 2 mmHg	26 (32.5%)	39 (48.8%)	65 (40.6%)
	> 2 mmHg	53 (66.3%)	35 (43.8%)	88 (55.0%)
Final (Week 52) Sleep Lab (N=61)	< -2 mmHg	5 (8.2%)	4 (6.6%)	9 (7.4%)
	-2 to 2 mmHg	22 (36.1%)	27 (44.3%)	49 (40.2%)
	> 2 mmHg	34 (55.7%)	30 (49.2%)	64 (52.5%)

IOP=intraocular pressure; mITT=modified Intent-to-Treat.
*Difference from In-Clinic calculated as Pre-negative pressure IOP value from sleep lab minus Pre-negative pressure IOP value from in-clinic. Thus, a negative number would be indicative of lower pre-NP IOP at the Sleep Lab.

***Table 32 (CP-X19)**: Mean OPAP Wear Times between Study Assessments, by Nightly Duration Category, in Study CP-X19 (mITT Population)*

Mean Wear Time (hours), n(%):	Week 0-6 (N=81)	Week 6-12 (N=74)	Week 12-26 (N=68)	Week 26-38 (N=65)	Week 38-52 (N=62)
> 8 hours	0 (0%)	0 (0%)	1 (1%)	1 (2%)	2 (3%)
> 6 hours	34 (42%)	30 (41%)	31 (46%)	32 (49%)	26 (42%)
> 4 hours	70 (86%)	61 (82%)	55 (81%)	54 (83%)	56 (90)
4 or fewer hours	11 (14%)	13 (18%)	13 (19%)	11 (17%)	6 (10%)
mITT = modified Intent-to-Treat					

*Please note that the sponsor updated the information related to "4 or fewer hours" in **Table 32** on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

***Table 33 (CP-X19):** Summary of Device Wear Time at Home in Subjects with NP Settings between -17 to -20 mmHg (Inclusive) for ≥ 26 Weeks*

Subject ID, hours:	Day 0 to Week 6	Week 6 to Week 12	Week 12 to Week 26	Week 26 to Week 38	Week 38 to Week 52	Device-Related AEs Reported
(b)(6)	6.0	5.7	6.1	6.5	6.5	None
	3.7	4.0	4.6	4.3	5.3	None
	2.8	2.0	2.2	2.0	2.5	Mild periorbital edema
	5.3	5.5	5.9	5.5	6.0	None
	7.2	7.8	7.8	7.6	7.0	None
	5.5	6.7	6.5	6.5	6.6	Mild periorbital edema, Mild symptoms & signs of dry eye
	6.2	5.9	5.8	5.4	5.9	None
	6.3	6.3	6.1	6.2	6.2	Mild periorbital edema

AE=adverse event.

***Table 34 (CP-X19)**: OPAP Wear Time during Sleep Lab Visits (Approximately Weeks 0 and 52)*

Visit Wear Time (hours):	Period of Wear Time	
	11:00 pm – 2:00 am Interval[1]	**2:00 am – 5:00 am Interval[2]**
Initial Sleep Lab, n	80	80
Mean ± SD	2.9 ± 0.3	2.8 ± 0.5
Median [Q1, Q3]	2.9 [2.7, 3.0]	2.8 [2.4, 3.1]
Min, max	2.1, 3.9	1.8, 4.2
Week 52 Sleep Lab, n	61	61
Mean ± SD	2.9 ± 0.3	2.6 ± 0.5
Median [Q1, Q3]	2.9 [2.7, 3.0]	2.4 [2.2, 2.9]
Min, max	2.0, 3.9	1.8, 4.2

CI=confidence interval; IOP=intraocular pressure; NP=negative pressure; Q1=first quartile; Q3=third quartile; SD=standard deviation.

Data reported as N; Mean ± SD; Median [Q1, Q3]; Min ,Max.

1. Difference between last pre-NP IOP time at the 11:00 pm measurement and the 1st pre-NP IOP time at 2 am measurement.
2. Difference between the last pre-NP IOP time at the 2 am measurement and the 1st pre-NP IOP time at 5 am.

***Table 35 (CP-X19)**: Ocular Adverse Events (Safety Population)*

Ocular Adverse Event	Study Eyes N=93			Control Eyes N=93		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any reported ocular AE	39	25	26.9%	17	13	14.0%
Anterior Basement Membrane Dystrophy	1	1	1.1%	1	1	1.1%
Conjunctival chalasis	0	0	0.0%	1	1	1.1%
Conjunctival hyperemia	4	4	4.3%	2	2	2.2%
Epithelial defect	1	1	1.1%	0	0	0.0%
Eye pain	4	3	3.2%	0	0	0.0%
Eye pain secondary to ocular trauma	0	0	0.0%	1	1	1.1%
Floater	1	1	1.1%	0	0	0.0%
Iritis	1	1	1.1%	1	1	1.1%
Lid edema	12	11	11.8%	1	1	1.1%
Lid erythema	2	2	2.2%	1	1	1.1%
Loss of BCDVA >= 10 letters from baseline	2	2	2.2%	2	2	2.2%
Meibomian gland dysfunction	1	1	1.1%	1	1	1.1%
Nuclear sclerotic cataract	1	1	1.1%	1	1	1.1%
Posterior vitreous detachment	2	2	2.2%	0	0	0.0%
Symptoms and signs of dry eye	6	5	5.4%	5	5	5.4%

Ocular Adverse Event	Study Eyes N=93			Control Eyes N=93		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Visual disturbance	1	1	1.1%	0	0	0.0%

% = n/N × 100%.
Includes events that occur on the date of randomization or later. An eye could report multiple events.
0 events were serious.

Table 36 (CP-X19): *Periorbital Adverse Events (Safety Population)*

Periorbital Adverse Event	Study Eyes N=93			Control Eyes N=93		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any reported periorbital AEs	20	17	18.3%	7	7	7.5%
Cherry hemangioma	0	0	0.0%	1	1	1.1%
Nasal abrasion	1	1	1.1%	0	0	0.0%
Periorbital contact dermatitis	4	4	4.3%	3	3	3.2%
Periorbital edema	12	12	12.9%	1	1	1.1%
Periorbital folds above eyebrows	1	1	1.1%	1	1	1.1%
Periorbital pain	2	2	2.2%	1	1	1.1%

% = n/N × 100%.
Includes events that occur on the date of randomization or later. An eye could report multiple events.
0 events were serious.

Table 37: *Ocular & Periorbital Adverse Events Reported After Randomization*

Ocular/Periorbital Adverse Event	Study Eyes N=93			Control Eyes N=93		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any device-related ocular and periorbital AE	44	32	34.4%	11	10	10.8%
Any device-related ocular AE	24	19	20.4%	5	4	4.3%
Conjunctival hyperemia	3	3	3.2%	1	1	1.1%
Eye pain	3	3	3.2%	0	0	0.0%
Lid edema	12	11	11.8%	1	1	1.1%
Lid erythema	2	2	2.2%	1	1	1.1%
Symptoms and signs of dry eye	3	3	3.2%	2	2	2.2%
Visual disturbance	1	1	1.1%	0	0	0.0%
Any device-related periorbital AE	20	17	20.4%	6	6	9.7%
Nasal abrasion	1	1	1.1%	0	0	1.1%
Periorbital contact dermatitis	4	4	4.3%	3	3	3.2%
Periorbital edema	12	12	12.9%	1	1	1.1%
Periorbital folds above eyebrows	1	1	1.1%	1	1	1.1%
Periorbital pain	2	2	2.2%	1	1	1.1%

% = n/N × 100%.
Includes events that occur on the date of randomization or later. An eye could report multiple events.
Device related consists of events considered Related or Possibly Related.

***Table 38**: Ocular and Periorbital Adverse Events Reported after Randomization by Severity (Safety Population)*

Ocular or Periorbital Adverse Event:	Study Eyes (N=93)			Control Eyes (N=93)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Ocular AEs	19 (20.4%)	5 (5.4%)	1 (1.1%)	12 (12.9%)	1 (1.1%)	0
Anterior Basement Membrane Dystrophy	1 (1.1%)	0	0	1 (1.1%)	0	0
Conjunctival chalasis	0	0	0	1 (1.1%)	0	0
Conjunctival hyperemia	3 (3.2%)	1 (1.1%)	0	2 (2.2%)	0	0
Epithelial defect	0	1 (1.1%)	0	0	0	0
Eye pain	1 (1.1%)	2 (2.2%)	0	0	0	0
Eye pain secondary to ocular trauma	0	0	0	1 (1.1%)	0	0
Floater	1 (1.1%)	0	0	0	0	0
Iritis	1 (1.1%)	0	0	1 (1.1%)	0	0
Lid edema	9 (9.7%)	1 (1.1%)	1 (1.1%)	1 (1.1%)	0	0
Lid erythema	2 (2.2%)	0	0	1 (1.1%)	0	0
Loss of BCDVA ≥ 10 letters from baseline	2 (2.2%)	0	0	2 (2.2%)	0	0
Meibomian gland dysfunction	1 (1.1%)	0	0	1 (1.1%)	0	0
Nuclear sclerotic cataract	1 (1.1%)	0	0	1 (1.1%)	0	0
Posterior vitreous detachment	2 (2.2%)	0	0	0	0	0
Symptoms and signs of dry eye	5 (5.4%)	0	0	4 (4.3%)	1 (1.1%)	0
Visual disturbance	1 (1.1%)	0	0	0	0	0
Periorbital AEs	14 (15.1%)	3 (3.2%)	0	7 (7.5%)	0	0
Cherry hemangioma	0	0	0	1 (1.1%)	0	0
Nasal abrasion	0	1 (1.1%)	0	0	0	0
Periorbital contact dermatitis	4 (4.3%)	0	0	3 (3.2%)	0	0
Periorbital edema	10 (10.8%)	2 (2.2%)	0	1 (1.1%)	0	0
Periorbital folds above eyebrows	1 (1.1%)	0	0	1 (1.1%)	0	0
Periorbital pain	1 (1.1%)	1 (1.1%)	0	1 (1.1%)	0	0

AE=adverse event; BCDVA=best-corrected distance visual acuity.
% = n/N × 100%.
Includes events that occur on the date of randomization or later.
Maximum severity of the event was used for eyes with multiple reports of the same
Device related consists of events considered Related or Possibly Related.

***Table 39 (CP-X19)**: Ocular and Periorbital Adverse Events Reported during Study Run-in Period*

	OS N=122			OD N=122			Combined N=244		
AE	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**
Any reported ocular AEs	2	2	1.6%	0	0	0.0%	2	2	0.8%
Meibomian gland dysfunction	1	1	0.8%	0	0	0.0%	1	1	0.4%
Myokymia	1	1	0.8%	0	0	0.0%	1	1	0.4%
Any reported periorbital AEs	3	3	2.5%	4	3	2.5%	7	6	2.5%
Nasal abrasion	0	0	0.0%	1	1	0.8%	1	1	0.4%
Periorbital contact dermatitis	1	1	0.8%	1	1	0.8%	2	2	0.8%
Periorbital edema	1	1	0.8%	1	1	0.8%	2	2	0.8%
Periorbital pain	1	1	0.8%	1	1	0.8%	2	2	0.8%

AE=Adverse event; OD=Oculus dexter (right eye); OS=Oculus sinister (left eye).

% = n/N × 100%.

Includes events that occur prior to the date of randomization, or in subjects who initiated OPAP run-in but are not included in the safety population. Because subjects had not been randomized to treatment, events are reported for the OD or OS eye, rather than Study Eye or Control Eye. A subject could report multiple events. No (0) events were serious.

*Please note that the sponsor provided additional information related to periorbital pain in **Table 39** on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

***Table 40 (CP-X19)**: Non-Ocular Adverse Events Reported During Study Run-In Period*

	N=122 Subjects		
AE	**# of Reports**	**# of Subjects**	**% of Subjects**
Any reported non-ocular AEs	6	5	4.1%
Back pain	1	1	0.8%
Basal cell carcinoma	1	1	0.8%
Headache (e.g., tension, migraine, sinus, etc.)	3	3	2.5%
severe left side facial swelling - abscess of 2 teeth	1	1	0.8%

AE=Adverse event.

% = n/N × 100%.

Includes events that occur prior to the date of randomization, or in subjects that initiated OPAP run-in but are not included in the safety population. A subject could report multiple events. No (0) events were serious.

*Please note that the sponsor provided additional information related to "severe left side facial swelling" in **Table 40** on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

Table 40: *Ocular and Periorbital Adverse Events Reported during Run-In Period, by Severity*

	OS (N=122)			OD (N=122)			Combined (N=244)		
Adverse Event:	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Ocular AEs	2 (1.6%)	0	0	0	0	0	2 (0.8%)	0	0
Meibomian gland dysfunction	1 (0.8%)	0	0	0	0	0	1 (0.4%)	0	0
Myokymia	1 (0.8%)	0	0	0	0	0	1 (0.4%)	0	0
Periorbital AEs	3 (2.5%)	0	0	2 (1.6%)	1 (0.8%)	0	5 (2.0%)	1 (0.4%)	0
Nasal abrasion	0	0	0	0	1 (0.8%)	0	0	1 (0.4%)	0
Periorbital contact dermatitis	1 (0.8%)	0	0	1 (0.8%)	0	0	2 (0.8%)	0	0
Periorbital edema	1 (0.8%)	0	0	1 (0.8%)	0	0	2 (0.8%)	0	0
Periorbital pain	1 (0.8%)	0	0	1 (0.8%)	0	0	2 (0.8%)	0	0

AE=adverse event; OD=oculus dexter (right eye); OS=oculus sinister (left eye).
% = n/N × 100%.
Includes events that occurred prior to the date of randomization, or in subjects who initiated OPAP run-in but are not included in the safety population. Because subjects had not been randomized to treatment, events are reported for the OD or OS eye, rather than Study Eye or Control Eye. A subject could report multiple events. Maximum severity of the event was used for eyes with multiple reports of the same event.

Table 41 (CP-X19)*: Ocular and Periorbital Adverse Events Reported during Run-In Considered Possibly, Probably, or Definitely Device-Related*

	OS (N=122)			OD (N=122)			Combined (N=244)		
Adverse Event:	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**
Any device-related ocular and periorbital AE	4	4	3.3%	4	3	2.5%	8	7	2.9%
Any device-related ocular AE	1	1	0.8%	0	0	0	1	1	0.4%

Adverse Event:	OS (N=122)			OD (N=122)			Combined (N=244)		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Myokymia	1	1	0.8%	0	0	0	1	1	0.4%
Any device-related periorbital AE	3	3	2.5%	4	3	2.5%	7	6	2.5%
Nasal abrasion	0	0	0	1	1	0.8%	1	1	0.4%
Periorbital contact dermatitis	1	1	0.8%	1	1	0.8%	2	2	0.8%
Periorbital edema	1	1	0.8%	1	1	0.8%	2	2	0.8%
Periorbital pain	1	1	0.8%	1	1	0.8%	2	2	0.8%

AE=adverse event; OD=oculus dexter (right eye); OS=oculus sinister (left eye).
% = n/N × 100%.
Includes events that occurred prior to the date of randomization, or in subjects who initiated OPAP run-in but are not included in the safety population. Because subjects had not been randomized to treatment, events are reported for the OD or OS eye, rather than Study Eye or Control Eye. A subject could report multiple events.
Device related consists of events considered Related or Possibly Related.

Table 42 (CP-X19): *Mean IOP Before and After Negative Pressure Application (Safety Population) (IOP Measured using Goldmann Applanation Tonometry)*

	Baseline (Day -14)		Day 0		Week 26		Week 52	
	Study	Control	Study	Control	Study	Control	Study	Control
GAT prior to NP								
N	93	93	93	93	68	68	62	62
Mean	14.7	14.8	14.4	14.2	14.7	14.8	14.4	14.0
SD	2.0	2.2	2.4	2.6	3.0	3.1	2.8	3.0
Median	14	14	14	14	15	15	14	13.75
Minimum	12	12	9	7.5	7	7	9	7.5
Maximum	20	21	21	22	24	22	21	20.8
GAT after NP								
N	93	93	93	93	68	68	62	62
Mean	14.1	14.2	13.9	14.0	13.7	14.3	14.2	14.0
SD	2.1	2.3	2.4	2.8	3.1	3.0	3.0	3.1
Median	14	14	14	14	14	14	14	13.5
Minimum	10	9	8	6	6	8.5	8.5	8
Maximum	19.5	20.5	20	22	24	22	21.5	21
Change in GAT after NP								
N	93	93	93	93	68	68	62	62
Mean	-0.6	-0.5	-0.4	-0.3	-1.0	-0.5	-0.3	0.0
SD	1.5	1.4	1.4	1.6	1.8	1.8	2.0	2.2
Median	-1	-0.5	-0.5	0	-0.5	0	0	0
Minimum	-4	-5.5	-6	-5.5	-6	-6	-7.5	-5
Maximum	4	4	3	3	3	3.5	3.5	7

Table 43 (CP-X19): *Visual Field Mean Deviation at Baseline (Day -14), Week 26, and Week 52 (Safety Population)*

Outcome	Baseline (Day -14)		Week 26		Week 52	
	Study	Control	Study	Control	Study	Control
N	93	93	68	68	62	62
Mean	-4.03	-3.67	-3.80	-3.45	-3.50	-3.35
SD	4.89	4.68	4.98	4.34	5.93	6.30
1st Quartile	-6.16	-5.60	-5.98	-5.39	-5.99	-4.57
Median	-2.61	-1.94	-2.21	-2.16	-2.29	-1.21
3rd Quartile	-0.63	-0.68	-0.57	-0.29	-0.58	-0.61
Minimum	-22.59	-20.37	-22.04	-16.90	-24.90	-28.15
Maximum	2.38	2.82	2.69	2.71	18.52	18.45
Not Reported	0	0	0	0	0	0
Total	93	93	68	68	62	62
Change from Baseline	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Improved ≥ 2.5 dB			8 (11.8%)	11 (16.2%)	11 (17.7%)	10 (16.1%)
Change <±2.5 dB	--	--	56 (82.4%)	52 (76.5%)	48 (77.4%)	49 (79.0%)
Worsened ≥ 2.5 dB	--	--	4 (5.9%)	5 (7.4%)	3 (4.8%)	3 (4.8%)
Not Reported	--	--	0	0	0	0
Total	--	--	68	68	62	62

N = Number of eyes with non-missing values at each visit. % = n/N × 100
Not Reported = Number of eyes with data not available at each visit.
*Visual fields from these subjects were evaluated by the U of Iowa Reading Center

Table 44 (CP-X19)*: OCT Mean RNFL Data*

RNFL Thickness:	Study Eye (N=62)	Control Eye (N=62)
Baseline	77.9 ± 13.6 µm	77.3 ± 14.5 µm
Week 52	77.9 ± 13.6 µm	77.5 ± 14.8 µm

OCT=optical coherence tomography; RNFL=retinal nerve fiber layer.

***Table 45 (CP-X19)**: Summary of CP-X19 Visual Field and OCT Data Analyzed by University of Iowa HC Visual Field Reading Center*

Time points for analysis of glaucoma progression	26 Weeks and 52 Weeks
Number of subjects with VFs at glaucoma progression time points	68 • 62 subjects completed the study with 52-Week follow-up • 6 subjects completed 26-Week follow-up, but exited prior to study completion
Total number of VFs	418
Total number of OCTs	392

Progression analyses performed	For all subjects who completed the 52-week study: • 52-Week VF alone • 52-Week VF + OCT For all subjects who completed 26-week follow-up, but did not complete the 52-week study: • 26-Week VF alone • 26-Week VF + OCT For all subjects who demonstrated 26-Week MD worsening ≥ 2.5 dB, all available VF + OCT ** (n = 7 subjects) For all subjects who demonstrated 52-Week MD worsening ≥ 2.5 dB, all available VF + OCT *** (n = 4 subjects)

**For subjects with 6-month MD loss ≥ 2.5 dB from Baseline, repeat VFs were collected at 9 months; these images were evaluated for evidence of progression (n = 7 subjects)
***For subjects with 12-month MD loss ≥ 2.5 dB from Baseline, repeat VFs were collected post-exit, and were evaluated for a final analysis of progression (n = 4 subjects)

***Table 46 (CP-X19)**: Study Assessments with 6- or 12-Month Analysis of Progression*

	n	# Eyes w/ Sufficient Scans	# Eyes w/ Insufficient Scans	# Eyes w/No Progression	# Eyes w/ Progression	# Eyes w/More Progression OD	# Eyes w/More Progression OS	# Eyes Indeter-minable
VF OD	68	51	17					
OCT OD	68	66	2					
VF OS	68	50	18					
OCT OS	68	67	1					
VF Alone Progression OD?				50	1	-	-	0
OCT + VF Progression OD?				51	0	-	-	0
VF Alone Progression OS?				49	1	-	-	0
OCT + VF Progression OS?				48	0	-	-	2
Has One Eye Progressed More?				48	0	0	0	0

***Table 47 (CP-X19)**: Summary of 52-Week Visual Field and OCT Data Analyzed by University of Iowa VFRC in Eyes with MD Loss ≥ 2.5dB or Glaucomatous Progression*

Subject ID	Eye	Eye Assignment[1]	VFRC Evaluation of Progression		
			VF alone	VF+OCT	Progression Relative to Contralateral Eye (Assessed by VF alone)[2]
VF MD Worsening ≥ 2.5 dB as compared to Baseline					
(b)(6)	OD	Treatment	No	No	No
	OS	Control	Indeterminable	No	Indeterminable
	OS	Treatment	Insufficient	No	Insufficient
	OD	Control	Insufficient	No	Insufficient
	OS	Treatment	No	No	Insufficient
	OD	Control	Insufficient	No	Insufficient
	OS	Treatment	Insufficient	No	Insufficient
	OD	Control	Insufficient	No	Insufficient
VF MD Worsening < 2.5 dB as compared to Baseline					
	OD	Treatment	**Yes**	No	**No**
	OS	Control	**Yes**	No	**No**

[1] VFRC readers were masked to treatment assignment. Eye assignment was determined by Equinox personnel after receipt of the VFRC report.

[2] "Insuffient" means the VF examination or OCT images were of insufficient quality for progression analysis. "Indeterminable" means VFRC readers, upon review of images considered "sufficient", were not able to determine if progression was present.

***Table 48 (CP-X19)**: Characteristics of Subjects in Study CP-X19 with Indeterminable Visual Field Progression, as Assessed by Visual Field Reading Center*

Subject ID	Eye	Eye Assignment	VFRC Evaluation of Progression		
			VF alone	VF+OCT	Progression Relative to Contralateral Eye
(b)(6)	OS	Control	No	Indeterminable	No
(b)(6)	OS	Control	No	Indeterminable	No

OCT=ocular coherence tomography; OD=oculus dexter (right eye); OS=oculus sinister (left eye); VF=visual field; VFRC=Visual Field Reading Center.

*Please note that the sponsor updated **Table 49** to remove 1 subject on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

Table 49 (CP-X10): *CP-X10 Study Assessments with 3-Mo Analysis of Progression*

	n	# Eyes w/Sufficient Scans	# Eyes w/ Insufficient Scans	# Eyes w/ No Progression	# Eyes w/ Progression	# Eyes w/ More Progression OD	# Eyes w/ More Progression OS	# Eyes Indeter-minable
VF OD	58	49	9					
OCT OD	58	56	2					
VF OS	58	51	7					
OCT OS	58	54	4					
VF Alone Progression OD?				46	1	-	-	2
OCT + VF Progression OD?				47	0	-	-	1
VF Alone Progression OS?				49	1	-	-	1
OCT + VF Progression OS?				48	0	-	-	2
Has One Eye Progressed More?				42	2	1	1	3

Table 50 (CP-X10): *Characteristics of Subjects in Study CP-X10 with Indeterminable Visual Field Progression, as Assessed by Visual Field Reading Center*

Subject ID:	Eye	Eye Assignment	VFRC Evaluation of Progression		
			VF alone	VF+OCT	Progression Relative to Contralateral Eye
(b)(6)	OD	Study	Indeterminable	Indeterminable	Indeterminable
	OS	Control	Indeterminable	Indeterminable	Indeterminable
	OS	Study	No	Indeterminable	Indeterminable
	OD	Control	Indeterminable	No	Indeterminable

Subject ID:	Eye	Eye Assignment	VFRC Evaluation of Progression		
			VF alone	VF+OCT	Progression Relative to Contralateral Eye

OCT=ocular coherence tomography; OD=oculus dexter (right eye); OS=oculus sinister (left eye); VF=visual field; VFRC=visual field reading center.

*Please note that the sponsor provided additional information related to an additional control eye in **Table 51** on February 15th, 2024, subsequent to their submission of DENXXXXX2/S001. Therefore, the FDA has not reviewed this change.*

***Table 51 (CP-X10):** Visual Field and OCT Characteristics for Subjects in Study CP-X10 with ≥ -2.5 dB MD Visual Field Loss at Day 90*

Subject ID:	Pre-Study Testing Date and Type	Study Testing Date and Type	Post-Study Testing Date and Type
(b)(6)	11/10/2015 – visual field 07/05/2016 – visual field 12/13/2016 – visual field 08/04/2017 – visual field	10/10/2019 – visual field and OCT 12/05/2019 – visual field and OCT 02/03/2020 – visual field and OCT	04/05/2021 – OCT 10/13/2021 – visual field
	07/15/2013 – OCT 06/18/2014 – OCT 02/07/2017 – OCT 06/26/2019 – OCT	07/15/2019 – visual field and OCT 09/05/2019 – visual field and OCT 10/31/2019 – visual field and OCT	None
	None	08/02/2019 – visual field and OCT 11/01/2019 – visual field and OCT 12/19/2019 – visual field and OCT	01/19/2021 – OCT 04/17/2021 – visual field 09/01/2021 – OCT
	None	12/04/2019 – visual field and OCT 01/15/2020 – visual field and OCT 03/11/2020 – visual field and OCT	06/09/2021 – visual field and OCT

MD=Mean Deviation; OCT=optical coherence tomography.

***Table 52 (CP-X19):** Proportion of Eyes with Week 52 In-Clinic IOP Reduction ≥ 20% During Negative Pressure Application (mITT Population)*

	Study Eye	Control Eye	Difference (95% CI)[1]	P-value[2]
IOP Reduction ≥ 20%	58.1% (54/93)	1.1% (1/93)	57.0% (45.4%, 66.2%)	<.0001

Eyes with missing values were assumed to be non-responders.
[1] Bonett, D. G. and Price, R. M. (2012), Adjusted Wald Confidence Interval for a Difference of Binomial Proportions Based on Paired Data, J Educational and Behavioral Statistics, August 2012, Vol. 37, No. 4, pp. 479–488.
[2] McNemar Test with a two-sided significance level of 0.05

***Table 53 (CP-X19)**: Proportion of Eyes with Week 52 Sleep Lab IOP Reduction ≥ 20% Reduction During Negative Pressure Application (mITT Population)*

	Study Eye	Control Eye	Difference (95% CI)[1]	P-value[2]
IOP Reduction ≥ 20%	63.4% (59/93)	3.2% (3/93)	60.2% (48.6%, 69.3%)	<.0001

Eyes with missing values were assumed to be non-responders.
[1] Bonett, D. G. and Price, R. M. (2012), Adjusted Wald Confidence Interval for a Difference of Binomial Proportions Based on Paired Data, J Educational and Behavioral Statistics, August 2012, Vol. 37, No. 4, pp. 479–488.
[2] McNemar Test with a two-sided significance level of 0.05

***Table 54 (CP-X19)**: Sleep Lab IOP Measurements by Excursion Method Measurements Prior to and During Negative Pressure Application (mITT Population)*

	Initial Sleep Lab		Final Sleep Lab	
	Study	**Control**	**Study**	**Control**
IOP (Excursion Tonometry with NP OFF)				
N	80	80	61	61
Mean	20.1	18.6	20.4	19.4
SD	2.5	2.5	2.5	2.3
1st Quartile	18.5	17.0	18.6	17.9
Median	19.8	18.5	20.3	19.3
3rd Quartile	21.8	19.8	21.7	20.8
Minimum	13.2	12.1	15.6	14.5
Maximum	28.1	28.0	27.9	25.4
95% CI	19.6,20.7	18.0,19.1	19.8,21.0	18.8,19.9
IOP (Excursion Tonometry with NP ON)				
N	80	80	61	61
Mean	12.5	16.8	12.4	17.7
SD	2.3	2.7	2.7	2.4
1st Quartile	10.9	15.1	10.4	16.0
Median	12.3	16.8	12.2	17.8
3rd Quartile	13.8	18.2	14.0	19.3
Minimum	7.9	10.6	8.1	12.3
Maximum	20.3	27.4	18.5	23.4
95% CI	12.0,13.1	16.2,17.4	11.7,13.1	17.1,18.3
Change in IOP from NP OFF to NP ON[1]				
N	80	80	61	61
Mean	-7.6	-1.8	-8.0	-1.6
SD	2.2	1.6	2.5	1.4
1st Quartile	-9.2	-2.6	-9.8	-2.7
Median	-7.1	-1.6	-7.8	-1.4
3rd Quartile	-6.1	-0.7	-6.3	-0.8
Minimum	-12.5	-8.4	-12.8	-5.6
Maximum	-2.9	1.5	-2.9	2.1
95% CI	-8.0,-7.1	-2.1,-1.4	-8.6,-7.4	-2.0,-1.3
Percent Change in IOP from NP OFF to NP ON[1]				
N	80	80	61	61
Mean	-37.5%	-9.4%	-39.1%	-8.4%
SD	9.0%	8.5%	11.1%	7.3%
1st Quartile	-43.8%	-14.0%	-48.4%	-12.9%
Median	-36.7%	-9.3%	-39.4%	-8.2%
3rd Quartile	-30.5%	-4.0%	-30.0%	-4.3%
Minimum	-59.3%	-41.4%	-58.7%	-26.5%
Maximum	-13.9%	10.1%	-14.4%	11.7%
95% CI	-39.5,-35.5%	-11.3,-7.5%	-42.0,-36.3%	-10.3,-6.5%
Percent Change in IOP Category				
Increase ≥ 40%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase ≥ 30% to < 40%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase ≥ 20% to < 30%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase ≥ 10% to < 20%	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (3.3%)
Increase > 0% to < 10%	0 (0.0%)	9 (11.3%)	0 (0.0%)	4 (6.6%)
No Change	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Decrease > 0% to <10%	0 (0.0%)	32 (40.0%)	0 (0.0%)	30 (49.2%)
Decrease ≥ 10% to < 20%	1 (1.3%)	32 (40.0%)	2 (3.3%)	22 (36.1%)
Decrease ≥ 20% to < 30%	17 (21.3%)	5 (6.3%)	13 (21.3%)	3 (4.9%)
Decrease ≥ 30% to < 40%	35 (43.8%)	0 (0.0%)	17 (27.9%)	0 (0.0%)
Decrease ≥ 40%	27 (33.8%)	1 (1.3%)	29 (47.5%)	0 (0.0%)

N = number of available measurements. % = n/N × 100%.

[1] Higher negative number is indicative of an improvement in IOP.

*The confidence intervals in **Table 55** are not based on pre-specified hypotheses or not adjusted for multiplicity.*

Table 55 (CP-X19): *M.ean IOP before and during OPAP Use with Calculated Intra-goggle*

	Baseline		Day 0		Week 26		Week 52	
Parameter:	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**
Excursion Tonometry IOP (TCPD Relative to Atmosphere) prior to Negative Pressure Application, IOP_p								
N	91	91	93	93	68	68	61	61
Mean	17.1	17.1	16.8	16.8	17.2	17.2	18.0	17.4
95% CI	16.5, 17.6	16.6, 17.6	16.3, 17.3	16.3, 17.3	16.6, 17.8	16.5, 17.8	17.2, 18.8	16.7, 18.2
SD	2.5	2.4	2.6	2.6	2.4	2.6	3.2	2.8
1st Quartile	15.3	15.3	14.8	15.3	15.8	15.3	15.5	15.5
Median	16.8	17.0	16.8	16.5	17.0	17.2	17.8	17.0
3rd Quartile	18.8	19.0	18.5	18.8	18.8	18.9	20.3	18.8
Minimum	11.8	11.0	11.3	10.5	11.5	11.3	12.0	13.0
Maximum	24.8	22.3	23.8	23.0	24.5	23.0	26.8	26.0
Programmed Negative Pressure, mmHg								
N	91	91	93	93	68	68	62	62
Mean	10.0	10.1	10.1	0.0	11.7	0.0	12.0	0.0
95% CI	9.5, 10.6	9.5, 10.6	9.5, 10.6	- , -	11.0, 12.5	- , -	11.0, 13.0	- , -
SD	2.6	2.7	2.5	0.0	3.1	0.0	3.8	0.0
1st Quartile	8.0	8.0	8.0	0.0	10.0	0.0	10.0	0.0
Median	10.0	10.0	10.0	0.0	12.0	0.0	11.5	0.0
3rd Quartile	12.0	12.0	11.0	0.0	14.0	0.0	14.0	0.0
Minimum	5.0	5.0	5.0	0.0	5.0	0.0	5.0	0.0
Maximum	17.0	18.0	16.0	0.0	20.0	0.0	20.0	0.0
Excursion Tonometry IOP (TCPD Relative to Atmosphere) during Negative Pressure Application, IOP_d								
N	91	91	93	93	68	68	62	61
Mean	11.2	11.2	10.7	16.0	10.9	16.9	11.4	16.8
95% CI	10.7, 11.6	10.7, 11.7	10.2, 11.2	15.4, 16.6	10.4, 11.5	16.2, 17.6	10.7, 12.2	16.0, 17.6
SD	2.2	2.3	2.4	2.9	2.4	2.9	3.0	3.0
1st Quartile	9.3	9.5	9.0	14.0	9.2	14.8	9.5	14.8
Median	10.8	10.8	10.5	16.3	11.0	16.8	11.3	16.3
3rd Quartile	12.5	13.0	12.5	18.0	12.8	18.9	13.0	18.8
Minimum	7.0	7.5	6.0	6.5	5.5	11.0	5.5	10.5
Maximum	17.3	17.5	16.0	21.5	16.8	22.3	20.8	26.3
TCPD Relative to Intra-goggle Space during Negative Pressure Application, IOP_e ($NP + IOP_d$)								

Parameter:	Baseline		Day 0		Week 26		Week 52	
	Study	Control	Study	Control	Study	Control	Study	Control
N	91	91	93	93	68	68	62	61
Mean	21.2	21.2	20.7	16.0	22.7	16.9	23.4	16.8
95% CI	20.4, 22.0	20.4, 22.1	19.9, 21.6	15.4, 16.6	21.8, 23.6	16.2, 17.6	22.3, 24.5	16.0, 17.6
SD	4.0	4.2	4.0	2.9	3.6	2.9	4.4	3.0
1st Quartile	18.5	18.3	17.8	14.0	20.2	14.8	20.0	14.8
Median	21.0	21.0	20.3	16.3	23.3	16.8	23.5	16.3
3rd Quartile	23.3	23.5	23.0	18.0	24.9	18.9	26.5	18.8
Minimum	12.5	13.3	13.0	6.5	14.0	11.0	14.8	10.5
Maximum	34.3	35.5	29.8	21.5	33.3	22.3	34.8	26.3
Percent Change in TCPD Relative to Intra-goggle Space, IOP_c (NP + IOP_d) during Negative Pressure Application*								
N	91	91	93	93	68	68	61	61
Mean	24.6%	23.8%	23.6%	-4.4%	33.0%	-1.4%	31.9%	-3.4%
95% CI (%)	21.1, 28.2	20.5, 27.1	20.6, 26.6	-6.6, -2.2	28.2, 37.8	-4.1, 1.3	26.6, 37.2	-5.8, -1.0
SD	17.2%	15.7%	14.6%	10.8%	19.7%	11.1%	20.9%	9.3%
1st Quartile	15.6%	13.3%	13.5%	-10.1%	21.7%	-8.1%	18.7%	-9.1%
Median	24.6%	23.8%	22.9%	-4.2%	33.5%	-0.7%	28.2%	-2.3%
3rd Quartile	35.3%	34.0%	35.6%	1.6%	45.9%	4.9%	44.0%	2.4%
Minimum	-26.2%	-16.2%	-15.2%	-57.5%	-19.4%	-28.2%	-4.8%	-24.5%
Maximum	64.6%	70.7%	57.2%	20.7%	101.8%	19.4%	77.1%	18.1%

CI=Confidence Interval; IOP_p=IOP relative to atmospheric pressure measured by Excursion Tonometry prior to NP application;
IOP_d=IOP measured relative to atmospheric pressure measured by Excursion Tonometry during NP application;
IOP_c=Calculated TCPD inside goggles during NP application; NP=negative pressure applied inside goggles;
TCPD=transcorneal pressure difference.
* = $(IOP_c\text{-}IOP_p)/IOP_p \times 100$.

*The confidence intervals in **Table 56** are not based on pre-specified hypotheses or not adjusted for multiplicity.*

***Table 56 (CP-X23)**: IOP at Each Timepoint (Study Eye and Control Eye)*

IOP (mmHg)	Baseline	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Post
Study Eye IOP							
Mean ± SD	**21.4 ± 4.3**	13.3 ± 3.6	15.0 ± 2.8	15.1 ± 3.4	14.1 ± 5.2	14.7 ± 4.4	23.1 ± 3.5
Percent change*		↓ 38%	↓ 30%	↓ 29%	↓ 34%	↓ 31%	↑ 8%
P-value**		P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P = 0.71
Control Eye IOP							
Mean ± SD	**20.4 ± 3.6**	17.6 ± 3.0	19.3 ± 2.8	20.8 ± 3.6	19.4 ± 4.3	20.1 ± 4.1	22.9 ± 4.4
Percent change*		↓ 14%	↓ 5%	↑ 2%	↓ 5%	↓ 1%	↑ 12%
P-value**		P < 0.05	P > 0.9	P > 0.9	P > 0.9	P > 0.9	P = 0.13

Table 1. Mean IOP measurements at various time points in the study and control eye. The percent change from baseline and the p-value comparing the value to baseline in shown for all time points following the baseline measurement. *The percent change is calculated in comparison to the baseline. **The p-value is calculated from a post-hoc paired t-test in comparison to the baseline value.

*The p-values in **Table 57** are not based on pre-specified hypotheses or not adjusted for multiplicity.*

Table 57 (CP-X24): *IOP and Reductions from Baseline during Negative Pressure Application (Evaluable Population)*

Patient, mmHg:	Baseline IOP	IOP at -10 mmHg NP	IOP Reduction at -10 mmHg	NP OFF_1	IOP at -20 mmHg NP	IOP Reduction at -20 mmHg	NP OFF_2
Patient 3	16.5	11.4	-5.1 (-30.9%)	12.7	8.2	-4.5 (-35.4%)	12.1
Patient 4	15.3	10.7	-4.6 (-30.1%)	16.1	8.1	-8 (-49.7%)	16.3
Patient 5	18.2	13.2	-5 (-27.5%)	18.9	9.7	-9.2 (-48.7%)	16
Patient 6	17.2	11.5	-5.7 (-33.1%)	16.1	8.3	-7.8 (-48.4%)	16.7
Patient 7	18	13.6	-4.4 (-24.4%)	17.1	10.7	-6.4 (-37.4%)	18.9
Patient 8	20.9	13.9	-7 (-33.5%)	20	9.8	-10.2 (-51.0%)	17.3
Patient 9	17.9	14.4	-3.5 (-19.6%)	16.6	10.6	-6 (-36.1%)	15.7
Patient 10	14.4	9.5	-4.9 (-34.0%)	12.7	6.5	-6.2 (-48.8%)	12.2
Patient 11	13.5	9.5	-4 (-29.6%)	13.2	6.7	-6.5 (-48.2%)	13.4
Patient 12	16.5	11	-5.5 (-33.3%)	14.7	7.8	-6.9 (-47.9%)	14.1
Patient 13	20.6	12.9	-7.7 (-37.4%)	18.6	10.1	-8.5 (-45.7%)	19.8
Patient 15	16.8	11.4	-5.4 (-32.1%)	14.4	7.5	-6.9 (-47.9%)	12.8
Patient 16	14.5	6.9	-7.6 (-52.4%)	13.3	2.6	-10.7 (-80.5%)	13.2
Patient 17	13.7	9.5	-4.2 (-30.7%)	14.5	6.6	-7.9 (-54.5%)	14.6
Patient 18	15.4	9	-6.4 (-41.6%)	14.6	3.8	-10.8 (-74.0%)	13.6
Patient 19	15.5	9.4	-6.1 (-39.4%)	14.4	5	-9.4 (-65.3%)	13.9
Patient 20	22.1	14.3	-7.8 (-35.3%)	18.7	8.2	-10.5 (-56.1%)	16.8
Mean	**16.9**	**11.3**	**-5.6 (-33.1%)**	**15.7**	**7.7**	**-8.0 (-51.2%)**	**15.1**

IOP=intraocular pressure; NP=negative pressure; OFF_1=first recovery period; OFF_2=second recovery period.
Note: IOP was measured every 0.5 seconds (500 milliseconds) using manometer connected to eye via fluid cannula, inserted temporarily during cataract surgery. Negative pressure was applied for approximately 30 seconds at -10 mmHg and then for another ~30 seconds at -20 mmHg, with approximately 30-second recovery period between NP applications. Values presented reflect average readings during the NP application and recovery periods. IOP reduction at -10 mmHg NP was calculated by comparing to Baseline IOP. IOP reduction at -20 mmHg NP was calculated by comparing to NP OFF_1.
Note: Three (3) subjects (patients 1, 2, and 14) had poor seals around cannula; therefore, manometric measurements were not possible and their data were not reported.

12. Figures

Figure 1: ***(A)*** *FSYX OPAP Pump;* ***(B)*** *FSYX OPAP Goggles*

Figure 2: *FSYX OPAP Pump- Manifold and Motor/Pumps with FSYX OPAP Goggles Connector (Section View)*

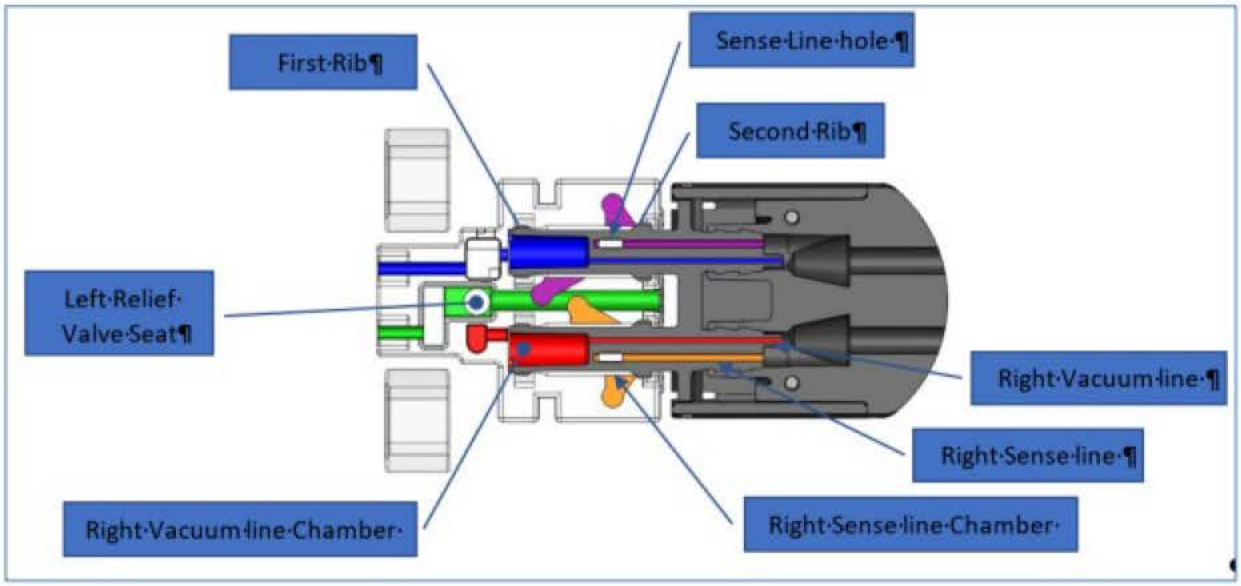


***Figure 3**: FSYX OPAP PUMP – Pneumatic Diagram*

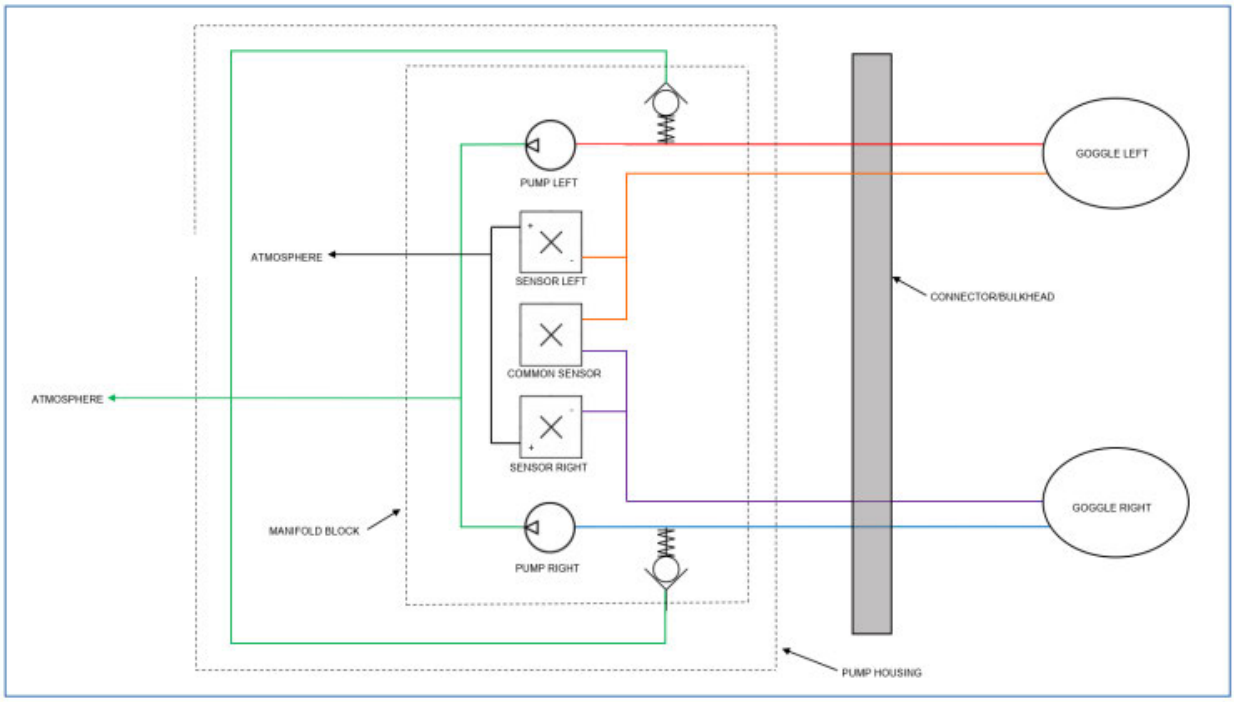


***Figure 4:** FSYX OPAP Goggles*

Item #	Part No.	Description
1	400-2083-001	Pivot, Gen 2
2	400-2111-001	Tubing, Para-tube
3	EQ-800-119	UV Adhesive
4	400-2073-001	Connector, Grip
5	400-2076-001	Connector, Tubing Insert
6	400-2075-001	Connector, Adapter
7	400-2074-001	Connector, Insert
8	EQ-800-076	Screw, 2-56 x .56
9	EQ-800-075	Nut, 2-56
10	400-2084-003	Tubing Single Lumen
11	400-2089-001	Headstrap
12	400-2114-001	Buckle, Headstrap
13	400-2115-001	Latch, Buckle
14	EQ-800-090	Pin, Buckle
15	400-2072-001	Strap Extension
16	400-2068-001	Seal, Pivot
17	400-2063-001	Lens, Drilled, Left
18	400-2063-002	Lens, Drilled, Right
19	EQ-800-115	Rivet
20	400-2123-002	Spring, A Bridge
21	400-2125-001	Washer, A Bridge
22	400-2129-001	Heatshrink, Bridge
23	400-2124-001	Grommet, Bridge Pins
24	400-2126-xxx	Seal, Gen2-B, Right
25	400-2126-xxxx	Seal, Gen-2B, Left
26	400-2071-002	Cap, Pivot Black
27	L-400-9047-xxx	Label, Goggle Gen2-B
28	EQ-800-080	RTV118 Clear Adhesive
29	400-2110-001	S-Collar, Tube
30	EQ-930-413	RFID tag

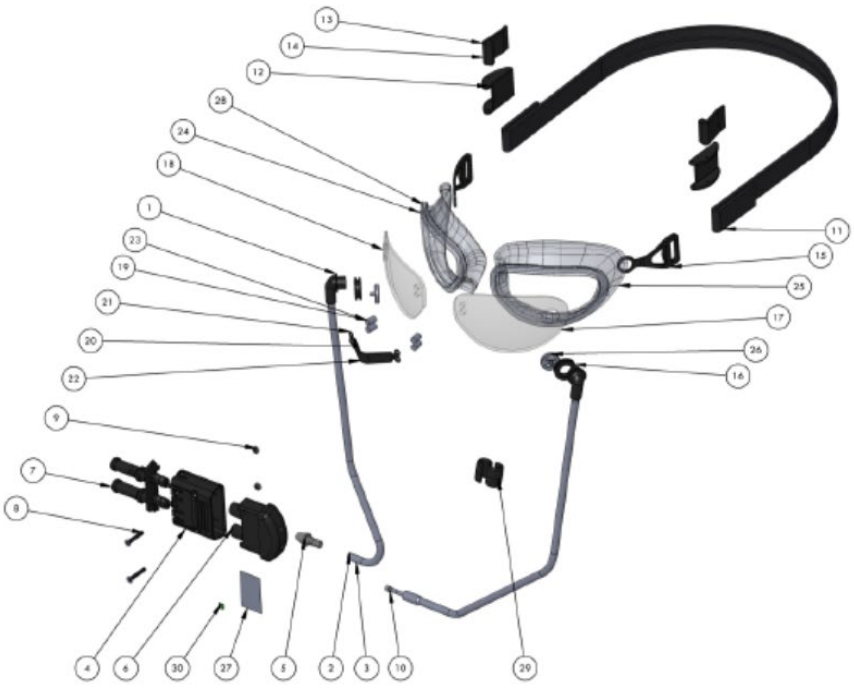


Figure 5: *FSYX OPAP Goggles- Nose Bridge Detail*

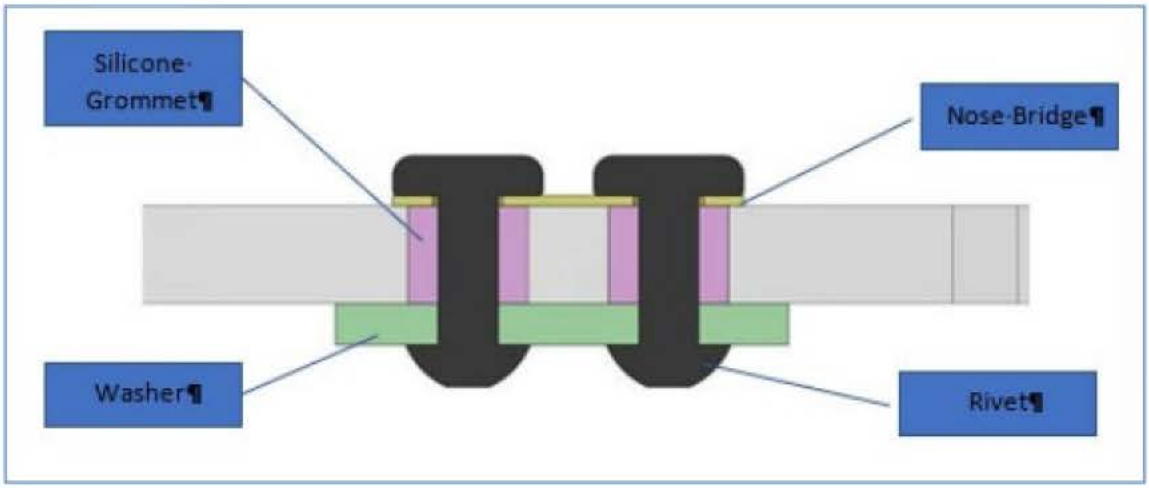


Figure 6: *FSYX OPAP Goggles- Lens and Pivot Detail*

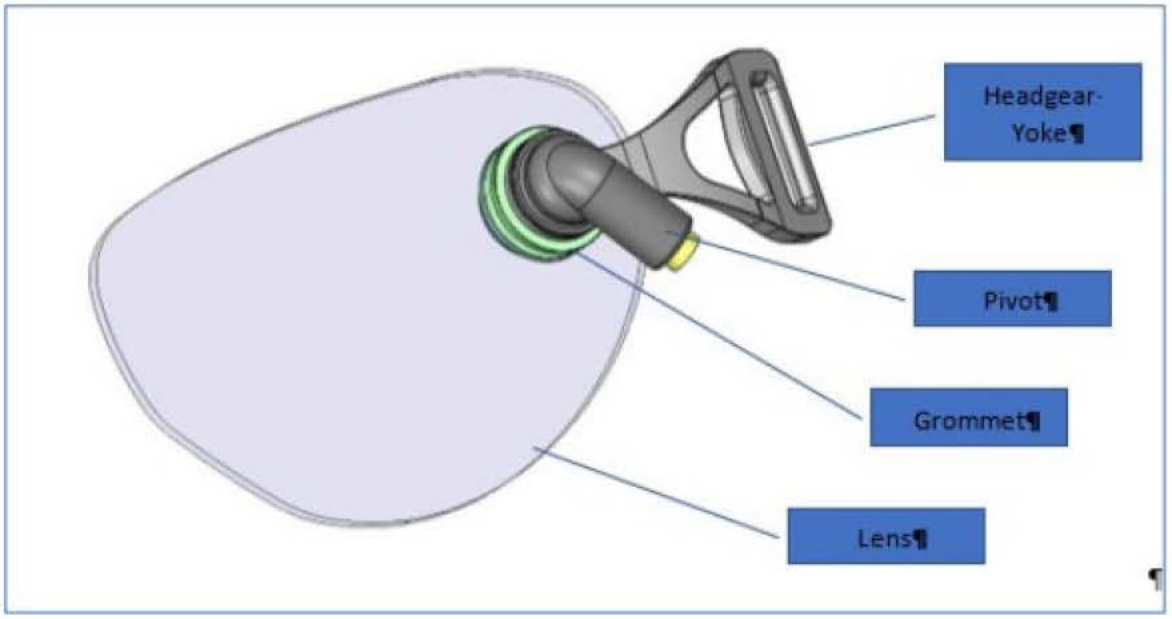


Figure 7: *FSYX OPAP Goggles- Lens and Pivot Cross-Section*

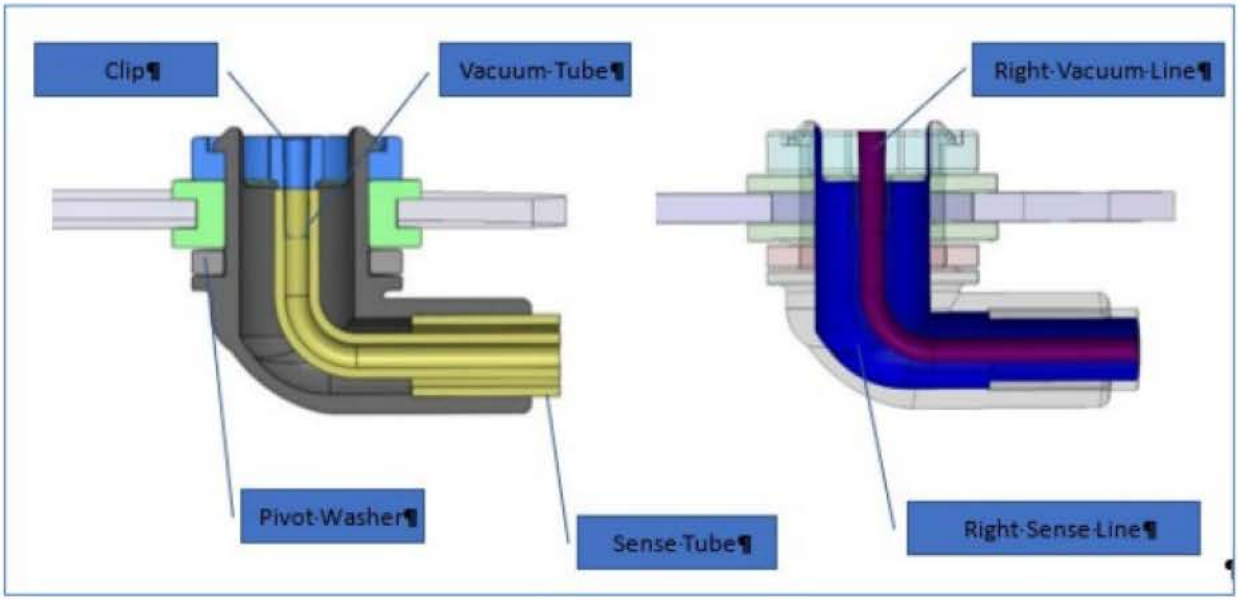


Figure 8: *Excursion Goggles (GEN 2)*

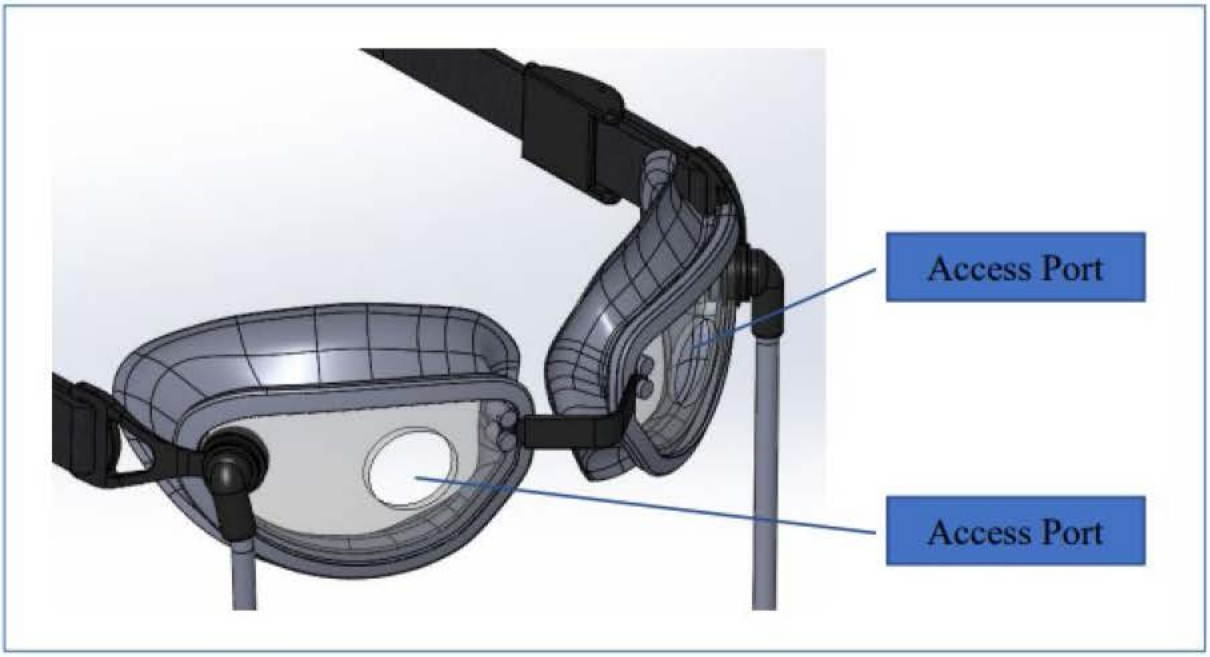


Figure 9: *Excursion Cartridge and Tono-Pen Cover*

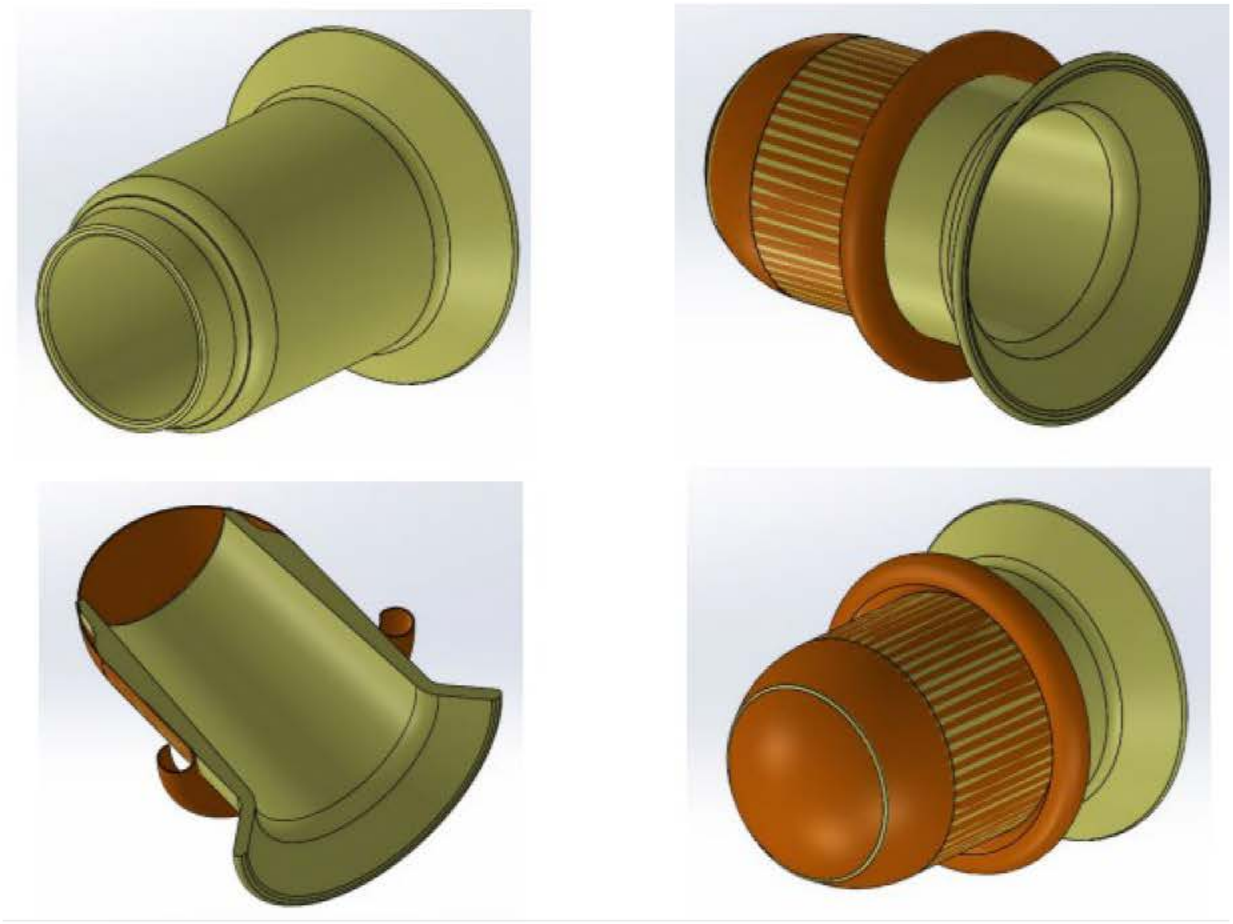


Figure 10: *Excursion Cartridge and Tono-Pen Cover Assembly and the Model 30 Tip (Blue in Picture)*

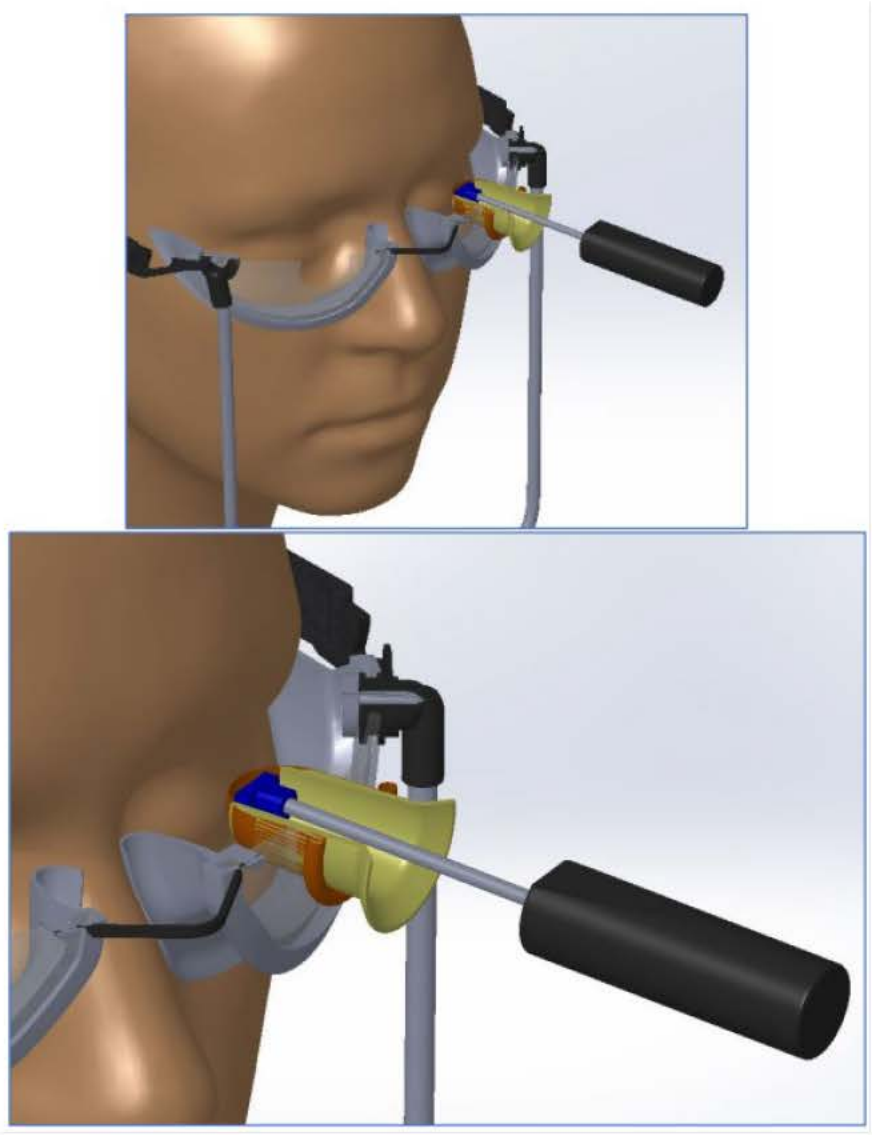


***Figure 11**: Specification of Different Pressures*

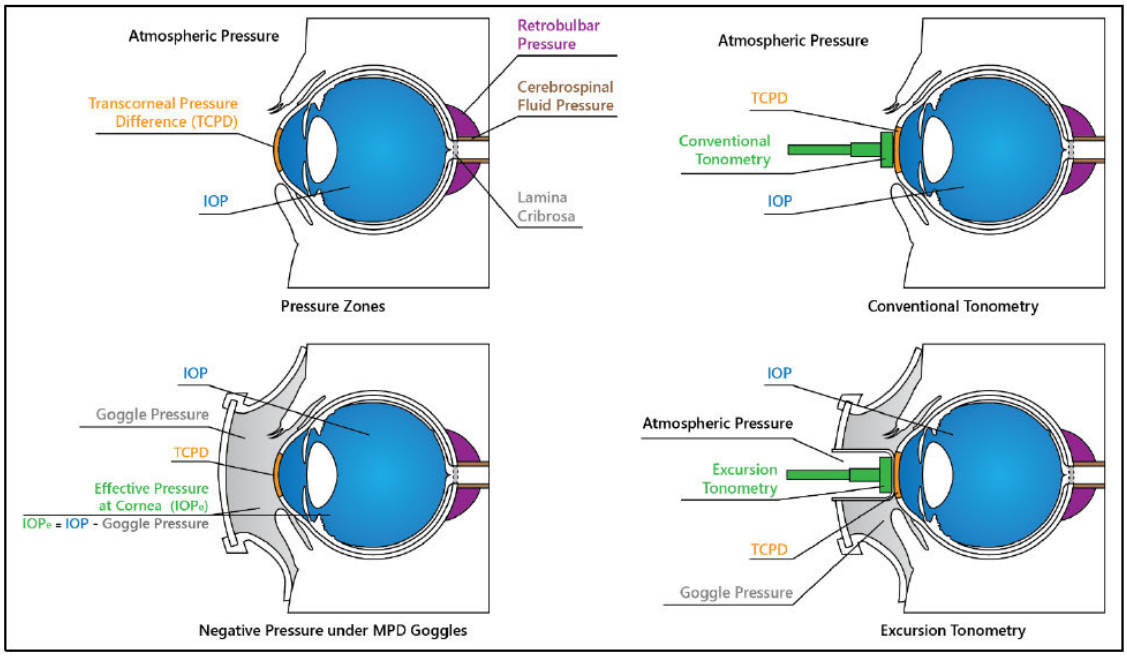


Figure 12 (CP-X19): *Study Visit Flowchart*

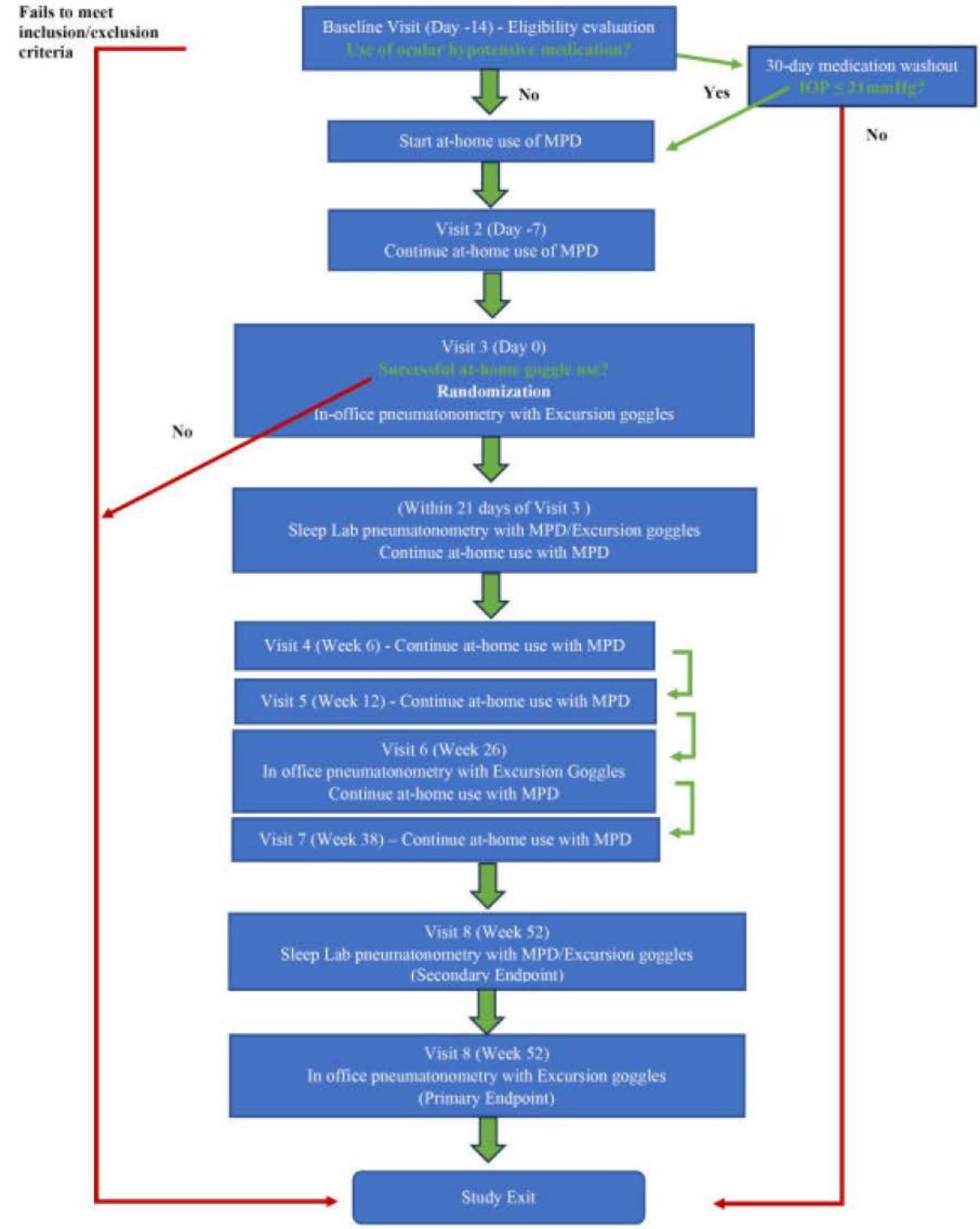


Figure 13 (CP-X19): *Recommended Reprogramming of Negative Pressure*

Model 30 Pneumatonometry from Visit 1	Program Pump
≤ 11 mmHg	- 5 mmHg
12 mmHg	- 6 mmHg
13-14 mmHg	- 7 mmHg
15-16 mmHg	- 8 mmHg
17-18 mmHg	- 9 mmHg
19-20 mmHg	- 10 mmHg
21-22 mmHg	- 11 mmHg
> 22 mmHg	- 12 mmHg

***The MPD is programmed by default to deliver 8-hour treatment sessions, and sleep wear is mandated during this next period.**

Figure 14 (CP-X19): *Proportion of Eyes with Week 52 In-Clinic IOP Reduction ≥ 20% During Negative Pressure Application (mITT Population)*

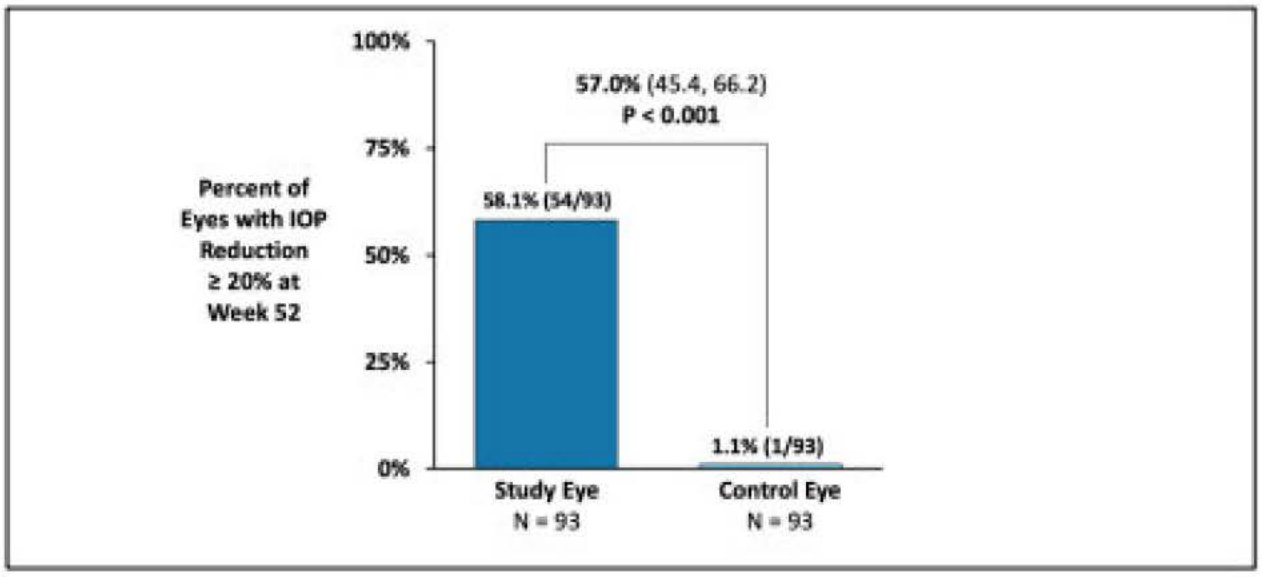


***Figure 15 (CP-X19)**: Proportion of Eyes with Week 52 Sleep Lab IOP Reduction ≥ 20% Reduction During Negative Pressure Application (mITT Population)*

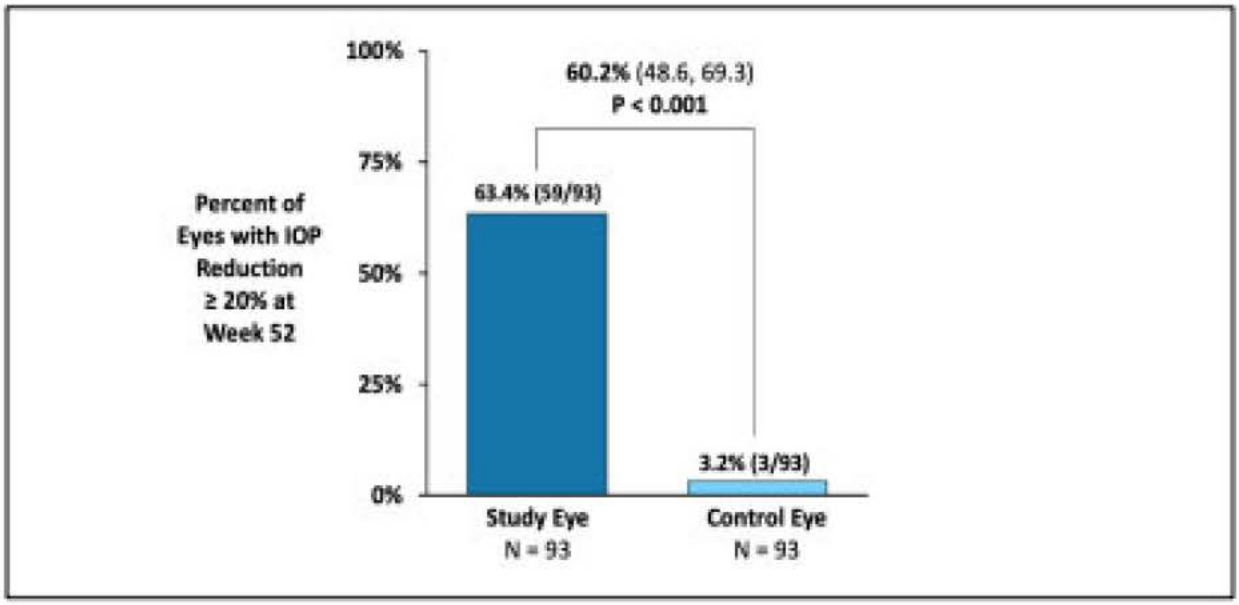


***Figure 16 (CP-X23):** The mean IOP in the Study and Control Eye*

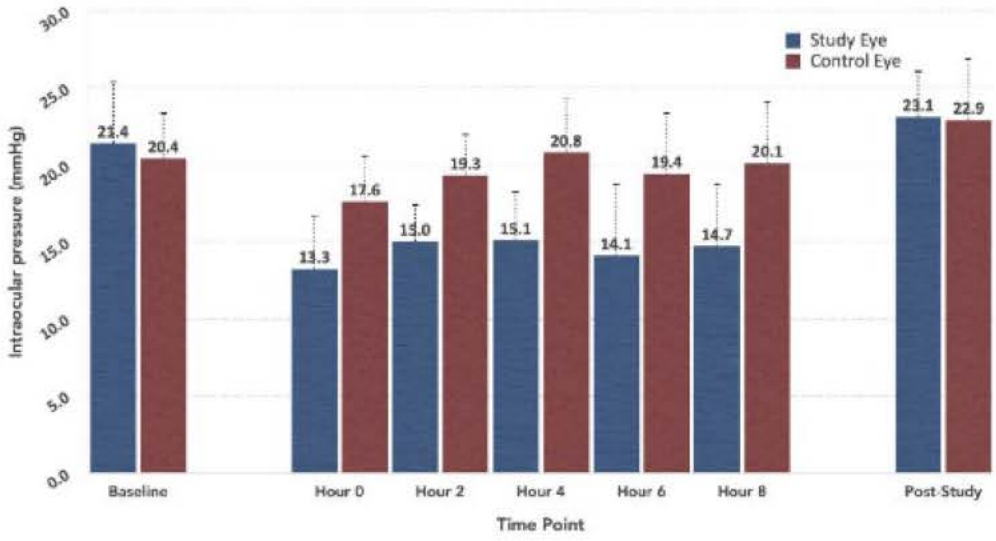
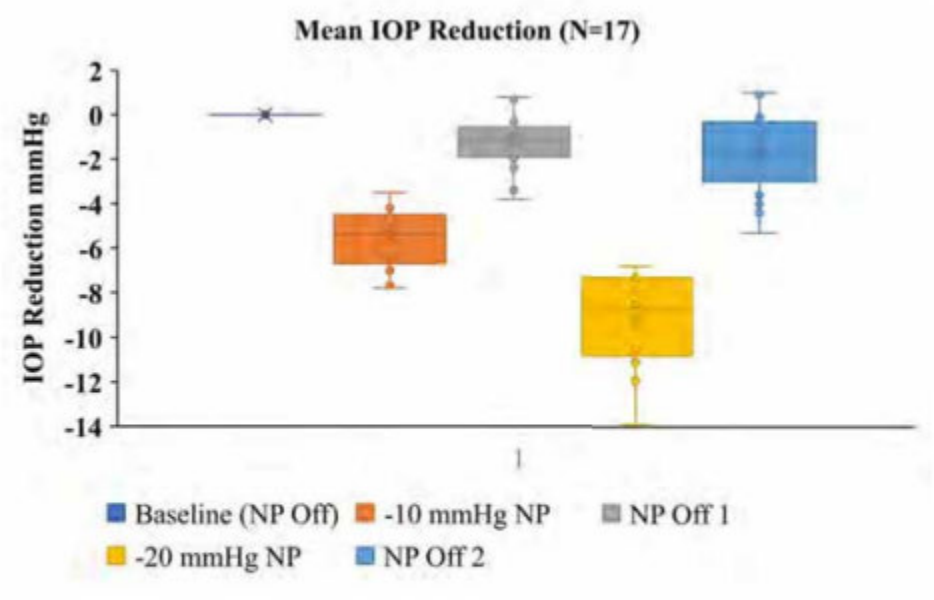


Figure 17 (CP-X24): *Mean IOP Reductions before and during NP Applications at -10 mmHg and -20 mmHg (Evaluable Population)*



IOP=intraocular pressure; NP=negative pressure
Note: IOP was measured every 0.5 seconds (500 milliseconds) using manometer connected to eye via fluid cannula, inserted temporarily during cataract surgery. Negative pressure was applied for approximately 30 seconds at 10 mmHg and then for another ~30 seconds at 20 mmHg, with approximately 30-second recovery period between NP applications. Values presented reflect average readings during the NP application and recovery periods. IOP reduction at -10 mmHg NP was calculated by comparing to Baseline IOP. IOP reduction at -20 mmHg NP was calculated by comparing to NP OFF 1.

13. Attachments

1. **DENXXXXX2/SXX1 (Responses to November 8, 2023 AINN Letter 1-5)**
2. **DENXXXXX2/SXX1 (Attachment CP-X19)**
3. **DENXXXXX2/SXX1 (Attachment 2-1, Provider Instructions for Use (IFU))**
4. **DENXXXXX2/SXX1 (Attachment 2-2, (Patient Instructions for Use (IFU))**
5. **DENXXXXX2/SXX1 (Attachment 4-2 (CONFIRM Study CP-X24 Report (Including Listings and Protocol))**
6. **DENXXXXX2/SXX1 (Attachment 4-3 Additional Information Product Insert)**
7. **DENXXXXX2 (Volume I)**
8. **DENXXXXX2 (Volume II)**
9. **DENXXXXX2/AXX3**
10. **DENXXXXX2/AXX4**
11. **DENXXXXX2/AXX5**
12. **DENXXXXX1 (Volume I)**
13. **DENXXXXX1 (Volume II)**
14. **DENXXXXX1 (AINN Letter, August 14, 2020)**
15. **DENXXXXX1/SXX1**
16. **DENXXXXX1/SXX1 (AINN Letter, January 6, 2021)**
17. **DENXXXXX1/SXX2**
18. **DENXXXXX1/SXX2 (DEND Letter, September 10, 2021)**
19. **QXXXXX4/SXX1**
20. **QXXXXX4/SXX1 (Feedback Letter)**
21. **QXXXXX4**
22. **QXXXXX4 (Feedback Letter)**
23. **QXXXXX3**
24. **QXXXXX2**
25. **QXXXXX1/SXX1**
26. **QXXXXX1/SXX1 (Feedback Letter)**
27. **QXXXXX1**
28. **QXXXXX1 (Interactive Request, October 23, 2017)**
29. **QXXXXX1 (Feedback Letter)**

14. Appendices

14.1 Appendix 1 – List of Abbreviations and Definitions of Terms

Abbreviation/Acronym	Term
AE	Adverse Event
BCDVA	Best Corrected Distance Visual Acuity
C:D	Cup-to-Disc Ratio
CDVA	Corrected Distance Visual Acuity
CRF	Case Report Form
dB	Decibel
DFE	Dilated Fundus Examination
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
GAT	Goldmann Applanation Tonometry
GEE	General Estimating Equation
IOP	Intraocular Pressure
LTFU	Lost to Follow-Up
MD	Mean Deviation
mITT	Modified Intent-to-Treat
mmHg	millimeters of mercury
OPAP	Multi-Pressure Dial
NP	Negative Pressure
NTG	Normal Tension Glaucoma
OCT	Optical Coherence Tomography
ONH	Optic Nerve Head
PSD	Pattern Standard Deviation
PP	Per Protocol
RNFL	Retinal Nerve Fiber Layer
Reference IOP	Refers to theoretical minimum IOP of 6 mmHg, the lowest IOP value for which the OPAP pump can be programmed
RMA	Returned Materials Authorization
SAE	Serious Adverse Event
SITA	Swedish Interactive Thresholding Algorithm
SLE	Slit Lamp Examination
SPK	Superficial Punctate Keratitis
SUN	Standardization of Uveitis Nomenclature
UADE	Unanticipated Adverse Device Effect